

Travelling in Towns is Necessary but not Impossible

THE Expenditure Committee of the House of Commons has done a useful if somewhat predictable job in its analysis of the problems of urban transport in British cities, published last week (Second Report from the Expenditure Committee, *Urban Transport Planning*, Vol. I, Report and Appendix, £0.42; Vol. II, Minutes of Evidence, £3.95; Vol. III, Appendices and Index, £0.73; HMSO). Unlike many other committees, the Subcommittee on the Environment and Home Office under Mr James Allason, MP has done a thorough job, collecting evidence not merely from the easily accessible ministries and the interested parties such as the Road Haulage Association, the Royal Automobile Club and even the British Cycling Bureau, but also from the local authorities and publicly supported transport organizations which live in the thick of the urban transport problem. The subcommittee's message is simple and a little stark—public transport must be encouraged, private transport must be discouraged and everybody must plan a little better. But the suggestions for improving public transport which the subcommittee's report puts forward are often imaginative. Only its proposals for restricting private transport sound hackneyed. And perhaps the most serious defect of an otherwise valuable report is that the subcommittee has failed to make a sufficiently tangible connexion between the problems of urban transport and the still larger and more durable problems of city planning.

The problem now confronting many British cities has long been familiar in the United States. Commercial vehicles, publicly owned buses and private cars compete for what road space there may be. The more the traffic grows, the greater is the congestion and the less efficient are the buses. The result is that travellers take to their private automobiles, the bus operators find their revenues dwindling and attempt to balance their books by making fewer journeys, which in turn implies that the service which they offer deteriorates and that increasing proportions of travellers are persuaded to take their cars to work. The result is all too apparent. The number of journeys by public buses in Britain has declined steadily in the past decade, from 13.7 thousand million in 1960 to 9.2 thousand million in 1970, while the average length of a journey has also declined. But the proportion of traffic on urban roads as represented by cars and taxis has similarly increased, by 22 per cent in half a decade. And there is nothing to suggest that these trends will quickly be moderated. To be sure, the statistics which the subcommittee has gathered make no allowance for the extent to which increasing congestion on the roads drives people from buses to the commuter railways, but there is at least a prospect that the major cities of Britain may in the foreseeable future find public buses as much a drain on local taxes and as unsatisfactory as they have become in North America.

The report is full of helpful suggestions for striking a

better balance. Special urban routes for buses, or traffic lanes reserved for their use, have obviously an important part to play. So too do schemes for making sure that buses travel more quickly, by giving them bigger engines, and schemes for encouraging a flattening of the peak travel hours by offering employers who ask their people to work eccentric hours a rebate on local taxes—one of the most obvious diseconomies of the present balance between private and public transport is that most people wish to travel in cities at about the same time, which increases congestion and decreases the use which is made of the capital locked up in buses. The subcommittee is also warm in its attitude towards unconventional methods of transport within cities—moving pavements, self-drive taxis and minibuses—but unfortunately indecisive. It would have helped if the subcommittee had been more forceful in urging that theorizing about other people's experiments should be replaced by research and development in Britain on these and other schemes.

By comparison, the argument about the need to restrict private transport on urban roads is dull. The subcommittee rightly says that more study needs to be carried out before it will be possible to implement fanciful schemes such as electronic pricing—a hobbyhorse of the National Roads Laboratory, which would install electrical devices in the roads and taxi-meters actuated by them in private cars so as to measure and to charge for the amount of nuisance caused by private transport in urban centres, a cure well calculated to be less palatable than the disease. Taxing permanent parking spaces in, for example, office buildings, may be sensible. There is less to be said for requiring that parking lots should not offer reduced rates to those who stay for longer periods or even for the restriction of off-street parking—if parking

Editor of *Nature*

Mr John Maddox, Editor of *Nature* since February 1966, will relinquish his post in the next few months and not later than June 30. Macmillan Journals Limited made the following announcement earlier this week.

"When John Maddox resigned as Managing Director of Macmillan Journals in June 1972, after what was described at the time as an honest but amicable difference of opinion, Macmillan agreed that he should be free to start an independent publishing organization while remaining Editor of *Nature*. More recently, however, Macmillan has reconsidered this decision, and as a result Mr Maddox will cease to be Editor of *Nature* when a successor is appointed later this year. Mr Maddox intends to remain in journalism and publishing."



spaces are suitably taxed, it is surely for those who pay the taxes to decide how best their investment should be made to work. The subcommittee rightly concludes that parking meters at present constitute a source of irritation, but this is again a reason for thinking that the encouragement of off-street parking would make a better policy. And although pedestrian precincts are delightful for those who want to walk in them, surely there is something to be said for first calculating the cost that will be incurred thereby. And it does not make sense to ask that there should be a moratorium on the construction of urban roads until the Department of the Environment has had a chance to reexamine each one of the schemes on which contracts have not yet been let—that is a prescription for more and not less chaos.

The economic analysis running through the report is patchy. In the past few years, the Department of the Environment has become extremely skilled at carrying out cost/benefit analysis of transport schemes, counting in its calculations the cost of people's time and being prepared to recognize that even schemes which operate at a commercial deficit, the new subway systems in London for example, should be counted as beneficial if the benefits exceed the cost. By this means, the Department of the Environment has apparently been persuaded that electric locomotives are better than diesel locomotives on many of the commuter lines in and out of London and many major cities. The trouble is that the kinds of cost/benefit analysis at present being undertaken are much less sophisticated than they should be. At a time when model-building and computer simulation are so fashionable, it is surprising that the department has not thought of constructing a model of British urban transport that would allow it to predict the consequences for the system as a whole of changes in the parameters which define it. Moreover, the economic analysis is still carried out with averages, yet it must be clearly apparent that many of the characteristics of urban transport are determined by the way in which different people put different values on their time and on travelling to work by car. What British cities, and those elsewhere, now need is some means of allowing those who are prepared to pay the full social cost of travelling in cities to do so, and if this means that more roads must be built, that is what urban authorities must stomach.

The weakest part of the subcommittee's report is, however, its implicit assumption that there is nothing much that can be done to reduce the demand for transport in cities by city planning. This, however, is a shortsighted view. It is true that the fabric of a city cannot be changed overnight, but in the long run, even within a decade or so, it is entirely possible that the need for people to thread their way through the intricate networks of streets by which modern cities are represented could be much diminished. The subcommittee is all for fiscal methods for restricting traffic. Should it not also consider fiscal methods for discouraging housing developments and office buildings which, by their location, are certain to add to the demand for transport? In Britain, where planning regulations are in principle quite strong, it is also entirely within the competence of local authorities to guide the development of cities in ways that will permit the efficient use of methods for the rapid movement of people from place to place. One possible solution to this problem is that of a cellular city, a network of compara-

tively dense townships connected by fast transport links and separated by open spaces. To fail to recognize that this or similar schemes offer the best permanent solution to the traffic problem is disappointing.

Lame Duck or White Elephant?

THE British and French governments will have only themselves to blame if the potential American customers for the Concorde aircraft fail to take up their options to buy, as now seems possible and even likely. From the beginning, the chief argument against the Concorde project has been economic. In the first place, the commitment of what has turned out to be £1,000 million of research and development expenditure by the French and British governments has been an imprudent use of scarce technical resources (and the fact that the original estimate, in 1962, was that research and development would cost merely £150 million is no excuse). In the second place, it has for several years been plain that the economic case for this particular supersonic aircraft was marginal, to say the best of it. The initial cost of each aircraft is now reckoned to be £23 million, while the passenger load (128 at the most) is so small that the operating costs (making allowance for depreciation) may be twice as great as the cost of carrying a passenger for a mile by the most efficient subsonic aircraft now in service. Especially now that airlines are under increasing pressure to show a profit on their present operations, it is understandable that they should be thinking of cancelling their options to buy Concorde.

What may be called the environmental case against supersonic aircraft is, by comparison, irrelevant. Whatever uncertainties there may be about the long-term effects of large-scale supersonic operations on the stratosphere, nobody would seriously suggest that the moderate fleet of Concords in prospect even before American airlines began turning sour would have measurable consequences, and although take-off noise and the supersonic boom are potentially serious extra nuisances, there is every likelihood that the operations of supersonic aircraft will be appropriately restricted. Indeed, the likelihood that night-time landings and take-offs will not be permitted will put at risk the hope of the aircraft manufacturers that each Concorde aircraft will be able to make four transatlantic crossings in each day, and thus further jeopardize the economics of Concorde. But in any case, in spite of all the theorizing of the past few years, nobody will dispute that the best way of discovering the environmental hazards of supersonic aircraft is to put a few into service. In this sense, the aircraft constructors can congratulate themselves on having carried out a public service, if at enormous cost to the taxpayers of Britain and France.

The practical question with which the British and French governments will be faced, if indeed American orders for Concorde fail to materialize, is to decide whether the programme of development should be continued and whether manufacture of commercial aircraft should be supported. The first thing to be said is that with a large part of the development cost already spent, there is a good case for completing the work and, in the process, for making a sufficiently close technical study of

what has been accomplished to permit a realistic assessment of the potential of supersonic commercial aircraft. Would it be feasible to make aircraft flying at Mach 2 or thereabouts sufficiently commodious to carry an economic payload? Is there a possibility that the range of Mach 2 aircraft should be substantially increased? Is the Concorde a possible starting point for the development of an aircraft flying at Mach 3, where the potential benefits of supersonic flight are greater but where other alloys and configurations may be needed? However much the British and French governments may now think that their fingers have been burned, it would be folly for them to overlook the value of the development work already carried out and paid for.

The more difficult question is that of how the aircraft should be brought into commercial service. It will be tempting to suppose that BOAC and Air France should be used as means of demonstrating that Concorde has commercial uses, and to provide the two airlines with a subsidy to keep the aircraft in service for the next few years. This, however, would be a mistaken policy. It is entirely reasonable that the governments should think of writing off the development cost, so that there should be no component of royalty in the price the airlines pay for their aircraft. It is, however, essential that the airlines should not be required to keep on their books uneconomic aircraft which are or become a hidden cost. In the past few months, BOAC, to its credit, has made much of the running in the campaign to bring about reduced fares across the North Atlantic (and it is hoped that the airline will soon extend its fare cutting to other fields). It would be intolerable if the two governments now foisted on their national airlines a scheme for putting Concorde into service which would have the effect of requiring other types of aircraft to shoulder some of the extra cost, for that would imply that ordinary airline passengers would be penalized so as to keep Concorde in the air. If the two governments eventually decide—and there is no reason why they should—that they will put Concorde into service even if the American carriers turn it down, their best course will be to set up a separate operating company, first agreeing to compensate BOAC and Air France for the traffic seduced away from their conventional operations. In such a situation, the true cost of this premature adventure into supersonic flight can be made plain for all to see.

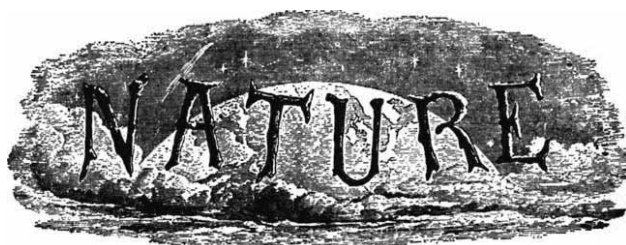
Secrecy in Science

MR AIREY NEAVE, the chairman of the House of Commons Select Committee on Science and Technology, performed an important public service on Monday, first by persuading the House of Commons that it should debate his committee's proposals for administering publicly supported research and development and then by making his own introduction to the debate on attack on the present traditions of secrecy within the government machine. Mr Neave is no doubt still smarting from the refusal of the government to make public the Docksey report on the National Research and Development Corporation, eventually published by the Select Committee itself, and the Vinter report on the future of nuclear power in Britain, still unpublished. But these are only the tips of

icebergs. The British government's administration of research and development in Britain is almost exclusively determined by the advice of committees which still operate in confidence and which have the effect not merely of obscuring the reasons why governments make particular decisions but also of preventing those individuals who take part in the advisory process, and who are usually the best informed, from engaging in the kind of public discussion of public issues which might bring enlightenment. Mr Neave is entirely right to emphasize the need for more open discussion.

Mr James Prior, the new Lord President of the Council, had only the weakest of replies on Monday. He held, somewhat implausibly, that it would be impossible to persuade distinguished scientists to give advice at all if they knew that what they said might eventually be published. But might it not be more sensible of him to turn the argument round, and to say that advice which is given only secretly is likely often to be unhelpful and even ill-considered? Worse still, there is of course a danger that if governments like the British neglect to cultivate the scientific community as an important constituent of public life, especially when both the government and the opposition are claiming that steps must be taken to make individuals feel more intimately involved in the making of decisions which affect them directly, the result will be still further to depress their spirits. It is reprehensible that decisions about science and technology should be made behind closed doors.

100 Years Ago



THE NATIONAL HERBARIA MEMORIAL

WE are glad to be able to lay before our readers the reply to the memorial to Mr. Gladstone, signed by so many eminent botanists, which appeared in *NATURE* for January 16. The answer is in every respect satisfactory:—

“Treasury Chambers, January 23, 1873

“Sir,—The Lords Commissioners of Her Majesty's Treasury have had before them your letter of the 3rd instant, and the Memorial enclosed in it from various gentlemen engaged in the pursuit of botany or in instruction therein, with respect to the transfer to the branch of the British Museum about to be constructed at South Kensington, of the scientific collections and library now existing at the Royal Gardens at Kew.

“Their lordships desire me to request that you will inform the memorialists that Her Majesty's Government have not formed the intention of removing the collection to South Kensington, and that should anything lead them hereafter to entertain the idea, they will take care that ample notice shall be given, and that the judgment of the persons most accomplished in botany shall be fairly weighed in the first instance.

“I am, Sir, your obedient servant,

“WILLIAM LAW

“The Rev. M. J. Berkeley, Sibbertoft,
“Market Harborough”

From *Nature*, 7, 243, January 30, 1873.

OLD WORLD

Water Council Decried

THE National Water Council—the proposed central point of the government's reorganization of the water services in Britain—came under renewed attack last week from the Water Resources Board in its ninth annual report. The bill to bring the changes into effect is due for publication this week.

Since the proposals in December 1971 to merge the twenty-nine existing river authorities and 1,350 drainage and sewerage authorities into ten large Regional Water Authorities, the Water Resources Board has repeatedly approved of the scheme's objects but condemned its methods in that no provision is made for a strong central body to control the activities of the water authorities. The Water Resources Board was one of the first to champion the theory that water services should be dealt with by a few large bodies with wide powers, rather than by many small bodies with limited interests, and Sir William Goode, the board's chairman, reiterates in the report that "this proposal is right and we welcome and support it".

But the board still believes, Sir William says, that a national water authority is needed to formulate and execute national water policy, subject to ministerial direction, to oversee and direct the authorities, to allocate capital investment, to run long-term planning and research and development and to promote major works such as the estuary storage schemes currently under consideration.

At present, the only central body proposed is a National Water Council which "will not in our view be equipped to do what needs to be done at the centre in the coming years".

The National Water Council will have the ten chairmen of the authorities as *ex officio* members and will also have coopted experts, but there are no provisions for an expert permanent staff such as that of the Water Resources Board. A central planning unit will be situated in the Department of the Environment, reporting to the minister and the council, but the Water Resources Board feels that such a unit will have divided loyalties.

The board is also critical of the proposals for the industry's research centre. The centre will not include the Water Pollution Research Laboratory, the only centre in Britain concentrating on water pollution work. The board argues that the laboratory should be

involved, together with the existing Water Research Association and with "the relevant parts" of the Water Resources Board. It should be governed and funded by the National Water Council.

But the board's objections are likely to go unheeded with publication of the bill so near. A change of heart at this stage is unlikely.

EURATOM

Decision in February

LAST week's meeting to discuss the European Commission's five year plan for Euratom produced the perennial deadlock that seems to haunt so many European cooperative ventures.

The commission's modified proposals allowed for a cut in the overall budget from 200 million units of account (one unit=one old dollar) to 185 million units and a considerable change in Euratom's hopes for non-nuclear research. Britain, France and the Netherlands, however, would only agree to projects costing 159 million units and the meeting ended unresolved with an agreement to discuss matters again on February 5.

Initial reaction in the commission is one of disappointment. The commission argues that to cut Euratom below the size it proposes will be effectively to close it down. But the British and French reasoning is that Euratom simply needs "pruning", and that cutting it down to the size they propose will not make the organization defunct. Britain is not against providing Euratom with a five year programme (it has existed on a year to year basis since 1968) but feels that those parts of the Euratom programme that have outlived their usefulness should be done away with.

The commission is hopeful, however, that the problem can in fact be settled at a political rather than a technical level. Both Britain and France want the individual projects examined in detail before they commit themselves to expenditure, but the commission, in the person of Mr Francois-Xavier Ortoli, its president, want the ministers first to accept the need for a common research programme.

One key to the problem is that the Euratom treaty is one of the founding treaties of the Common Market, so that the closure of Euratom would result in the removal of one of the com-

munity's *raison d'être*—a situation that the commission sees as intolerable and which gives it hope that a satisfactory compromise might be reached next month. If Euratom's future has to be sorted out at a purely political level then the commission believes it has a much higher chance of survival.

At last week's meeting Mr Ortoli and Mr Théo Lefevre, the Belgian science minister, both asked the ministers to take a political approach to the problem, pointing out that Euratom's expenditure is only 0.19 per cent of the total that the nine members of the EEC spend on their individual research efforts.

PARLIAMENT

Agreeing to Differ

THE differences of opinion between the government and the Select Committee for Science and Technology were aired once again in the House of Commons on Monday of this week. In a debate which asked the House to take note of the select committee's four reports on research and development and the government's observations on these reports, Mr Airey Neave, chairman of the select committee, called on the government to review its decision not to appoint a minister for research and development.

Mr Neave pointed out that the European Community is seeking a "comprehensive policy on scientific research and technological development". He asked whether the government, if it agrees that there has to be a community policy on research and development, will then consider having a national policy itself.

The government in its white papers turned down the select committee's request for an industrial advisory committee and Mr Neave confessed that he was not clear as to why it had done so. Mr Neave said that the view expressed to the select committee that industry should do all its own research and development is false, and that "a programme of government research and development will have to be maintained by the United Kingdom if it is to remain competitive in the next 25 years".

This suggestion is one of the "main themes behind some of the recommendations of the select committee", said Mr Neave but Mr James Prior, Leader of the House of Commons, said

that he was worried that industry had not made full use of all the research which had come from the research councils in the past few years. Mr Prior said that he had been told that if Britain stopped all its research for ten years and merely applied the results of discoveries already made then a high growth rate would still be achieved. Mr Prior did add, however, that he was not advocating this course of action.

UNIVERSITIES

Five Year Plan

UNIVERSITIES will have less to spend on each student during the next five years with the average amount being two per cent down on that spent in 1972-73, according to the University Grants Committee. This is the upshot of the government's plans for education announced in December (*Nature*, **240**, 372; 1972).

The money available to universities for each student has increased during each of the last two five-year plans although the estimated ten per cent increase per student planned to occur between 1967 and 1972 only amounted to half this because the number of students increased by more than had been planned.

The UGC in its memorandum released last week offers advice to universities on how the grant for the next five years should be allocated between departments. Although the universities are free to spend the block grant they receive as they choose, the UGC hopes that the guidelines it proposes will be adhered to.

The committee recommends that during the next five years, universities should allocate their grants according to Table 1 which is assessed on the basis that the average for the different subjects is 98 per cent of that spent at present.

The UGC stresses that all universities will not have to decrease their spending by two per cent per student and that some will therefore have to decrease spending by more than this. The committee points out that medical schools are in a state of rapid development caused especially by Lord Todd's report on medical schools in London, published in the late 1960s. The UGC states that clinical medical departments outside London should be able to develop with the same level of support as they now enjoy.

The committee says that the recommended relative rates of spending shown in Table 1 have been arrived at by considering the "present pressures on the different disciplines and the way in which growth to 1976-77 will affect them". The fact that pressure in recent years has been on arts places rather

Table 1 Recommended Distribution of Money for different Subjects during 1972-77*

Medicine and Dentistry	102
Social and Business Studies	101
Architecture and Planning	101
Education	100
Arts	99
Veterinary Science	99
Mathematics	98
Agriculture and Forestry	97
Engineering and other Technologies	96
Physical and Biological Studies	95

* Percentage of present expenditure per student.

than science made the government decide in the education white paper that the present ratio of arts to science of 45/55 be changed to 47/53 by 1976-77. Thus, says the committee, "it would appear that the room for economies of scale as growth proceeds are . . . more evident in the sciences than in the arts subjects, and this consideration (among many others unconnected with student numbers) has conditioned the committee's approach to the determination of the block grant".

The UGC also makes the following suggestions to the universities.

- That computer sciences be strongly developed as well as statistics, operational research, and numerical analysis.

- That undergraduate computing courses be further encouraged.

- Electronic, electrical and production engineering and engineering design be encouraged. Also that broad-based research training and undergraduate courses in the technologies be favoured.

- Money allocated to engineering and physical sciences departments be

more than the recommended average of 95 or 96, because these departments have many costly research programmes.

- The UGC would welcome the development of undergraduate courses with an education component combined with another subject such as mathematics or science.

SPACE

Pie in the Sky

BRITAIN and the United States have completed formal arrangements for the National Aeronautics and Space Administration to launch the Department of Trade and Industry's Earth satellites on a contract basis. The agreement is simply the formalization of an understanding reached in 1971 after Britain had decided to scrap Black Arrow (see *Nature*, **232**, 363; 1971).

The first satellite to be launched by NASA under the agreement will be X4, Britain's second technology satellite, which is scheduled for March 1974. The contract for the launch was signed on January 11 and the price DTI is to pay is about £1.25 million. The satellite is designed to prove a new 3-axis attitude control system, as well as a new solar array and a number of experimental sensors.

X4 will go up on a Scout launch vehicle, but DTI's next launch may be on a Delta rocket if the Geostationary Technology Satellite (GTS), on which Hawker Siddeley Dynamics and Marconi are currently working, goes ahead. It is at present scheduled for late 1976, but plans for the satellite may be changed if the plans laid by Mr Michael Heseltine, Minister for Aerospace and Shipping, for a European Space Agency come to fruition.

Advisory Board for the Research Councils

THE following are the members of the Advisory Board of the Research Councils which has replaced the Council for Scientific Policy.

Professor Sir Frederick Dainton (chairman), Dr Lee's Professor of Chemistry, University of Oxford; Sir Kenneth Berrill, chairman, University Grants Committee; Dr W. R. Boon, managing director, Plant Protection Ltd (ICI); Dr R. H. L. Cohen, chief scientist, Department of Health and Social Security; Sir Brian Flowers, chairman, Science Research Council; Dr J. A. B. Gray, secretary, Medical Research Council; Professor F. H. Hahn, professor of economics, University of Cambridge; Dr W. M. Henderson, secretary, Agricultural Research Council; Professor Sir Alan Hodgkin, president of the Royal Society; Dr P. E. Kent, exploration manager, British Petroleum Co. Ltd; Mr D. J. Lyons, director general of research, Department of the Environment; Dr I. Maddock, chief scientist, Department of Trade and Industry; Professor R. C. O. Matthews, chairman, Social Science Research Council; Dr A. W. Merrison, vice-chancellor, University of Bristol; Professor W. S. Peart, professor of medicine, St Mary's Hospital Medical School, University of London; Dr H. C. Pereira, chief scientist, Ministry of Agriculture, Fisheries and Food; Dr O. Simpson, chief scientific officer, Cabinet Office; and Professor F. H. Stewart, chairman, Natural Environment Research Council.

NEW WORLD

More Shuffling of the Pack

by our Washington Correspondent

SWEEPING changes in the federal science policy machinery are expected to be announced by President Nixon this week. At the beginning of the week, the final touches were being put to a reorganization plan which will abolish the Office of Science and Technology, the President's Science Advisory Committee and the position of Science Adviser to the President and give the director of the National Science Foundation responsibility for advising the White House on policies for civilian science and technology. The task of advising the President on policies for military research and development will be transferred from the OST to the National Security Council, the chairman of which is Dr Henry Kissinger.

The reorganization plan will give Dr Guyford Stever, director of the National Science Foundation, the dual responsibility of managing a federal agency and offering advice to the White House on general policy matters. But his advice will not go directly to the President but to the President's Economic Adviser, Dr George Shultz, who has recently been given the role of coordinating US economic policy (see *Nature*, 241, 158; 1973). The effect will, therefore, be to shift responsibility for advising on science policy from the President's Science Adviser, who at least had direct access to the President, to the head of a small government agency who has access only to a presidential adviser.

As for the OST, its demise has been predicted since Dr Edward E. David, who was director of the office and Science Adviser to the President, left Washington in a surprise move earlier this month (see *Nature*, 241, 82; 1973). Some of its staff are likely to be transferred to the National Security Council, others to the National Science Foundation, a few may go to the Office of Management and Budget, and the rest will be out of a job.

Sources close to the White House said this week that the initial idea will be for the National Science Foundation to be concerned chiefly with advice on civilian science policy, but advice on biomedical research policies will continue to come from the National Institutes of Health. There is some chance, however, that Dr Stever's role may eventually be broadened to include these fields as well.

The National Science Board, the

policy-making body which helps direct the work of the National Science Foundation, is likely to take on some of the functions that were the responsibility of the President's Science Advisory Committee. But its advice will go first to Dr Stever, then to Dr Shultz, then to the President and it will not concern itself directly with military research and development. The National Science Board has published reports on an annual basis for the past few years on various aspects of science policy, graduate education and manpower planning for example, but they have had little effect on the shaping of national policies. Whether it will have more effect in future will depend in part on the effectiveness of Dr Stever.

The new role envisaged for the National Science Foundation will in fact give it the functions that were assigned to it when the foundation was set up by congressional charter in 1950. The National Science Foundation Act gave the NSF the responsibility for evaluating the programmes of other agencies in the science field. But when the launching of Sputnik sent shock waves through the federal government, it was felt that the director of the NSF would not be able to provide strong oversight over mission-oriented science agencies, and President Eisenhower established the post of Science Adviser to the President directly in the White House. And five years later, President Kennedy set up the Office of Science and Technology, and gave it the task of coordinating the activities of all the federal agencies concerned with science and technology.

One reason why the wheel has turned full circle is that since 1968 the National Science Foundation has broadened its activities in supporting applied research—an amendment to the National Science Foundation Act, sponsored by then Representative Emilio Q. Daddario and Senator Edward M. Kennedy, gave the foundation authority to support applied as well as basic research. It was felt that this broader role enabled the National Science Board and the director of the foundation to take a better view of the whole federal involvement in science and technology. One factor which was unclear at the beginning of the week, however, is how Dr Stever will be able to resolve a possible conflict of interest. On the one hand, he will be director of an agency which receives federal support and on the other

he will be advising the White House on how it should be distributing funds to science agencies.

Clean Air Act

by our Washington Correspondent

RESIDENTS of Los Angeles were given a nasty shock last week. They were told by the federal government that if the city's smog-laden air is to be cleaned up enough to comply with the Clean Air Act, they will have to cut their use of automobiles by more than 80 per cent during the summer and equip their cars with pollution control devices costing between \$200 and \$400.

Those extreme measures were proposed last week by the Environmental Protection Agency which was under a court order to devise a scheme for meeting the primary air quality standards—which are designed to protect health—in Southern California by 1977. What the agency has proposed is a system of petrol rationing, beginning in 1975, which by 1977 would reduce petrol consumption in the Los Angeles basin by 82 per cent between May and October, when pollution is at its worst.

If the scheme is carried out, it will quickly bring the area to a grinding halt, for Southern California is virtually built around the automobile—there are 10 million people in the Los Angeles basin and 6 million cars, and because the city is such a sprawling metropolis it is almost impossible to get from one part to another without a car. It is also said that apart from its numerous drive-in banks, restaurants and cinemas, Los Angeles even boasts a drive-in funeral parlour.

A federal requirement which would probably wreck the economy and lifestyle of Southern California should be sufficient to provoke a mass revolt. But, although there has been some outspoken opposition to the plan, few people have taken it seriously. Even Mr William D. Ruckelshaus, Administrator of the Environmental Protection Agency, made it clear when he unveiled the plan that he was only offering such a drastic measure because he was ordered by a court to come up with a scheme which would definitely meet the standards. His scheme may be unworkable, but it would comply with the Clean Air Act.

The EPA's plan will be the subject of public hearings in Los Angeles in the next few months and, as Ruckelshaus

pointed out last week, it will at least compel people to face the consequences of cleaning up Los Angeles air. In effect, the EPA has said to residents in Southern California that this is the cost of bringing air quality to a level at which it no longer presents a hazard to health, and the cost must now be weighed against the benefits.

If the costs are considered unacceptable, the most likely recourse would be to amend the Clean Air Act to give Southern California more time to comply. That would be the responsibility of Congress, and it would open the floodgates to special pleading from other cities having a tough time meeting the standards.

It can be argued, however, that the Los Angeles basin is a special case. For one thing, it is the unfortunate possessor of a sunny climate and for another it is flanked on three sides by mountains—two factors which combine to cause the infamous Los Angeles smog. What happens is that there are frequent temperature inversions over the basin in the summer, and the air hangs over the city, trapped in by the mountains. The six million cars in the basin continue pouring exhaust gases into the stagnant air, and in the presence of sunlight, hydrocarbons react with oxides of nitrogen to form the brown smog of photochemical oxidants which makes the surrounding mountains disappear in the afternoon.

The air quality standards imposed by the Clean Air Act would restrict the concentration of photochemical oxidants to 0.08 parts per million, but in 1970 that standard was exceeded in the Los Angeles area on more than 250 days. And the growth of the automobile population in the area—between 3 and 4 per cent a year—is continuing to exacerbate the problem.

In most areas in the United States, the air quality standards can be met by placing emission controls on stationary sources of pollution and by the stringent emission standards required for cars by 1975. But it soon became clear that in Los Angeles such measures would hardly make a dent in the air pollution problem and that some form of transportation controls would have to be imposed. The EPA reckons that by 1977, even with controls on stationary sources and automobile exhausts, some 691 tons of reactive hydrocarbons would be poured into the atmosphere each day; to achieve the national standard of 0.08 parts per million of photochemical oxidants, the agency calculates that hydrocarbon emissions must be reduced to 161 tons a day.

As for the petrol rationing proposal, the EPA has not spelled out how it should be implemented, but suggests either that motorists should be given coupons or that production should be

rationed. In addition, catalytic converters must be fitted to the exhaust systems of all cars made since 1965, to convert carbon monoxide and hydrocarbons into carbon dioxide and water, devices must be attached to prevent the escape of fumes from the petrol tank and carburettor, and all cars and lorries in fleets of ten or more must be converted to run on low polluting fuels such as natural gas.

What happens next? It seems that two avenues are open if it is decided that the EPA's scheme would result in unacceptable social and economic dislocation. Either the EPA can propose a less drastic scheme, on the basis of submissions to the public hearing, which would only go part of the way towards meeting the standards, or Congress can amend the Clean Air Act to provide an exception for Southern California. Both options would, however, have serious implications for the future of the Act. In the meantime, the state of California, whose original plan for meeting the standards was rejected by the EPA, has until February 15 to draw up a revised plan of its own. Clearly, however, it will be no more successful in devising an acceptable plan than the EPA.

If the EPA decides to relax its scheme

without waiting for Congress to amend the Clean Air Act it would break the law and be liable to a court action. In that case, its lawyers would probably argue that the act is unenforceable in the specific situation in Los Angeles, and if such a plea were successful, the agency could be given some leeway by the courts. The EPA would, however, be skating on thin legal ice. The other alternative—Congressional action to provide relief for Southern California—would probably be instigated by California's two senators, John Tunney and Alan Cranston. Both have denounced the EPA's plan, and Tunney has suggested that more attention should be paid to mass transportation as a means of reducing automobile traffic in Los Angeles. But so far neither has shown any indication of offering an amendment to the Clean Air Act.

Whichever alternative is adopted, Ruckelshaus can be certain that he will be assailed by representatives from other cities pleading for special treatment as well. Twenty-seven other areas in the United States must impose some type of transportation controls if they are to meet the standards imposed by the Clean Air Act, and although their controls would be minor in comparison to the Los Angeles plan, they could

NUTRITION

What's in a Name?

by our Washington Correspondent

THE Food and Drug Administration has proposed sweeping changes in the labelling and promotion of food products in the United States. Described by Dr Charles C. Edwards, Commissioner of the FDA, as "the most significant change in food labelling since food labelling began", their purpose is chiefly to give consumers more extensive information about the nutritional value of the food they eat. The proposals have been greeted with mixed reactions from food manufacturers, some of whom have complained that they will increase the price of foods, and from consumer groups, some of which have suggested that the proposed regulations do not go far enough.

Companies which fortify their foods with nutrients, or which make advertising or labelling claims about nutritional value, will have to specify on the labels the number of calories and the quantity of protein, carbohydrates and fat in each serving. In addition, levels of vitamins and minerals must be specified in terms of the recommended daily allowance (RDA) rather than the minimum daily requirement. RDA levels have been established by the FDA largely on the basis of advice from the

National Academy of Sciences. They are higher than the minimum daily requirement levels, and should be less misleading.

Aware of the fact that many companies now list ingredients in the most inconspicuous manner possible, the FDA is also proposing that nutritional labelling should be standardized and placed in a particular location on the package.

The agency has also proposed that all products marketed as dietary supplements must contain between 50 and 150 per cent of the RDA for certain specific vitamins and minerals. If they contain less than 50 per cent of the RDA for these vitamins and minerals, they must be classified as foods, or if they contain more than 150 per cent, they must be marketed as drugs and meet stiff tests of effectiveness.

The regulations have taken ten years to draw up, and manufacturers have been given until December 31, 1974, to comply. The most severely affected companies will be those which are attempting to cash in on the present "health food" fad in the United States by making false or exaggerated claims about the nutritional value of their foods. No longer will they be able to claim that natural vitamins are more effective than synthetic vitamins, or that inadequate or insufficient diet is caused by the soil in which a food is grown.

plead hardship with some conviction. They have until February 15 to come up with their plans.

But the Los Angeles smog is not Ruckelshaus's only worry in relation to the Clean Air Act. Acute shortages of low-sulphur fuels in the United States are likely to prevent some states from putting into effect their plans for meeting the sulphur oxides standards prescribed by the act, and the situation is likely to be exacerbated by the so-called energy crisis.

A study conducted by the Mitre Corporation for EPA has come to the conclusion that there will be insufficient quantities of low-sulphur fuels available, particularly in the Midwest, to allow all the plans to be put into effect, and it suggested that some states which have relatively pure air should be deregulated. The effect would be to increase sulphur dioxide pollution in those states, although it would not increase enough to exceed the primary air quality standards. Moreover, the "energy crisis", which has rapidly taken over from the "environmental crisis" as the chief topic of conversation in the United States, is likely to harm the environmentalist bandwagon in general and the Clean Air Act in particular.

Exceptionally cold weather earlier this month caused such a shortage of heating oil that schools and offices were closed all over the Midwest, and other areas were preparing for power breakdowns. President Nixon is due to outline the Administration's policies for coping with the energy crisis in a message to Congress in February or March, and it is widely expected that he will call for a greater reliance on coal for electricity generation—a move which would not help solve the problem of the shortage of low sulphur fuels.

But Ruckelshaus, for one, can be expected to fight hard to preserve the Clean Air Act from moves to weaken it. He has already refused to give automobile manufacturers extra time to develop emission control devices, in spite of a recommendation from the National Academy of Sciences, and his hard-nosed management of the EPA during his first two years in the job has won him wide respect from all sides. He said last week that he would like more flexibility in administering the provisions of the Clean Air Act, but that the act is "a great success". Just "because 5 per cent of it may not be working doesn't mean you ought to junk the whole act", he said.

CIGARETTES

Smoking and Health

from our Washington Correspondent

SINCE 1964 the US Public Health Service has published seven reports surveying the evidence linking cigarette

smoking to disease and premature death. All have found that cigarette smoking is not only a major cause of lung cancer and chronic bronchitis, but that it is also associated with illness and death from chronic bronchopulmonary disease, cardiovascular disease and other illnesses. The latest in the series, published last week, is no exception. According to Dr Merlin K. DuVal, who resigned last month as Assistant Secretary for Health, it "confirms all these relationships", and it also has disquieting things to say about the effects of smoking on foetal development and mortality. The report also takes a look, for the first time, at brands of little cigars which are becoming popular in the United States. It concludes that if they are smoked in the same manner as cigarettes, they are likely to have the same effect on the health of the smoker.

As for the effects of smoking on pregnancy, the report points out that in 1970 one-third of American women of child-bearing age were cigarette smokers and it is estimated that the percentage of American women who smoke during pregnancy is "in the neighbourhood of

20 to 25 per cent". A large foetal population is therefore at potential, though preventable, risk.

The report comes to the following conclusions about the effects of smoking on the foetus:

- On the average, a woman who smokes during pregnancy runs nearly twice the risk of delivering an infant of low birth weight as that of a non-smoker, and there is strong evidence of a dose-response relationship.
- Recent studies suggest that "cigarette smoking is most strongly associated with a higher stillbirth rate among women who possess less favourable socio-economic surroundings or an unfavourable previous obstetrical history".
- There is a "strong, probably causal" association between cigarette smoking and higher late foetal and infant mortality.
- No conclusions can be drawn about any relationship between smoking during pregnancy and congenital malformation.
- Smoking does not seem to influence the sex ratio of newborn infants.

Short Notes

Institute of Medicine

THE Institute of Medicine, an associate institution of the National Academy of Sciences, announced last week that it has been given a grant of \$300,000 by the Richard King Mellon Foundation in support of its general operations. The grant will be paid in three annual instalments, and it brings the total amount granted to the institute for the next three years to \$1.5 million.

Reshuffle at NIH

TOP officials at the National Institutes of Health were shuffled around last week in a manner resembling a strange game of executive musical chairs. Dr John F. Sherman, Deputy NIH Director for the past four years, was promoted to Acting Director of NIH. Dr Robert Q. Marston, who was fired last month as NIH Director, was appointed Acting Director of an NIH institute, the National Institute of Neurological Diseases and Stroke (NINDS), and Dr Edward F. MacNichol, NINDS Director since 1968, left NIH partly of his own volition.

The moves suggest that Sherman will probably be given the full directorship of NIH, although there is still a possibility that President Nixon could appoint somebody else. But Marston's appointment is a temporary one, to ensure administrative continuity while a new NINDS director is chosen. Marston was informed last month that

President Nixon had accepted his *pro forma* resignation as NIH Director, but no reasons have yet been publicly stated. MacNichol, on the other hand, resigned on his own initiative. It was revealed, in September 1971, that he had spent several months at Woods Hole while drawing government travel funds of \$25 a day—a fact which led to a review by the General Accounting Office and by the NIH head office of government travel grants—but MacNichol retained his post without any change of status.

The reshuffle therefore puts Sherman in authority over his former boss and Marston in a dead end job.

US/USSR Cooperation

COOPERATION between the United States and the Soviet Union on environmental problems is continuing apace. This week, a joint working group met in Moscow to discuss wildlife conservation, and the Council on Environmental Quality, which is looking after the US end of the cooperative agreement, announced last week that fifteen other joint meetings have been arranged for 1973 on topics ranging from air and water pollution to earthquake prediction. Meanwhile, the chief cooperative agreement between the United States and the Soviet Union on science and technology is theoretical. The first meeting of the Joint Commission which was set up by the agreement has twice been put off, and Dr Edward David's departure from the Office of Science and Technology has left nobody officially in charge of the US end of the agreement.

NEWS AND VIEWS

Phytoagglutinins and Mammalian Sperm Penetration

IN mammals, no less than in lower vertebrates and invertebrates, the means whereby the spermatozoon enters the egg to effect fertilization has long been a puzzle. First attachment occurs as the result of an "effective" collision by the spermatozoon, and this seems to be a necessary preliminary to penetration of the investment. The high degree of specificity in the process of attachment constitutes a bar to hybrid fertilization. At the same time, by no means every spermatozoon that becomes attached succeeds with penetration, for this too is generally reserved for spermatozoa of the same, or a closely related, species. Furthermore, in mammals particularly, the egg investment (zona pellucida) reacts so as to become more resistant after the entry of the first spermatozoon, and thus the frequency of multiple or polyspermic fertilization is minimized. Polyspermy is a normal feature of fertilization in some organisms, such as birds and reptiles, but in mammals it leads inevitably to maldevelopment and, nearly always, death of the growing embryo.

Clearly the properties of the zona pellucida are highly important for the initiation of normal development, and many attempts have been made to elucidate the nature of the zona pellucida and the mechanisms of sperm attachment and penetration. Early work showed the zona pellucida to be a neutral or weakly acidic mucoprotein which could be crudely characterized by its staining properties, and its solubility following treatment with enzymes and other agents. After sperm penetration, changes were recorded which seemed to have been associated with the zona reaction. But none of these observations helped materially towards a satisfactory understanding.

On page 256 of this issue of *Nature*, Oikawa, Yanagimachi and Nicolson describe experiments with plant agglutinins, and their report could well signal a new and fascinating phase of research on sperm-egg interactions. In essence, these authors find that treating hamster eggs with wheat germ agglutinin not only reduces sperm attachment to the zona pellucida but prevents their penetration of this structure, and inhibits its dissolution by several otherwise highly effective enzymes. Treatment increases the light-scattering property of the outer surface of the zona pellucida, suggesting a change in molecular organization there. These effects are prevented if the specific substrate, N-acetyl-D-glucosamine, is present in sufficient concentration, implying the presence on the surface of the zona pellucida of oligosaccharides containing terminal residues of this kind.

Oikawa *et al.* propose that the phytoagglutinin forms cross-links between the oligosaccharide chains of adjacent glycoprotein molecules, and thus prevents dissolution of the coat by experimentally applied enzymes. Cross-links would also render attachment sites unavailable and would tend to counter the action of the postulated "zona lysis" which is held to function by digesting a path for the spermatozoon through the zona pellucida. Certain other phytoagglutinins have a similar blocking action; this was found to be true particularly for the *Ricinus communis* agglutinin, which attaches to β -D-galactose-like residues,

and the *Dolichos biflorus* agglutinin, which attaches to N-acetyl-D-galactosamine-like residues, but rather less so for concanavalin A, which attaches to α -D-mannose-like residues. One can therefore infer that a variety of saccharide residues in the surface of the zona pellucida are critically involved in the process of fertilization.

The identity of the saccharide residues on the zona pellucida could well determine the species specificity of sperm-egg attachment. They would constitute "recognition" sites such as seem likely to be involved in cell aggregation during embryonic development or following artificial disaggregation in culture. A basic difference would, of course, be that the recognition sites exist on plasma membranes, from which the zona pellucida differs in several particulars. Nevertheless there are some important similarities. Just as the plasma membranes of cells that are undergoing transformation exhibit changes in surface properties, the sperm permeability of the zona pellucida is capable of alteration with the occurrence of the zona reaction and with the ageing of the egg.

A homology between attachment sites of phytoagglutinins and antibodies seems undoubted, and the observations of Oikawa and his colleagues are complementary to those of Shivers, Dudkiewicz, Franklin and Fussell (whose unpublished paper they cite) who blocked the fertilization of hamster eggs by prior treatment with a rabbit antibody raised against hamster ovary. The effect was shown to be attributable to antibodies against the zona pellucida, and the block was associated with a change in the optical properties of the outer layer of this coat. As with the wheat germ agglutinin, treatment with antibody protected the zona pellucida from dissolution by protease. Whether the antibody would block attachment of the phytoagglutinin, and vice versa, has yet to be determined. *A priori*, such a result might be anticipated.

There are good signs that with their homogeneity and high specificity the phytoagglutinins could prove invaluable new tools for the investigation of gamete structure and function in mammals.—C. R. A.

Fixes on Radio Sources

OPTICAL identification becomes possible for some types of radio object as soon as radio source catalogues have errors of position better than 1 arc s r.m.s. in both right ascension and declination. For the identification to be certain, an optical accuracy of better than 1 arc s in each coordinate is required, and, further, if the object is condensed and nearly stellar then it must be either a blue object or a galaxy fainter than 19 magnitude. On page 261 of this issue of *Nature*, Gent *et al.* report a revised identification of eleven radio sources, three of which have now been identified with stellar objects that are neutral in colour. The certainty of identification has been made possible by the increased accuracy to 0.5 arc s r.m.s. in each coordinate using measures obtained from the interferometer at the Royal Radar Establishment. What will

a spectroscopic investigation of these sources reveal about their nature? Will they turn out to be quasars with high redshifts or an entirely new class of object?

The earliest attempt to obtain accurate optical positions of radio sources was made in 1963 by R. Griffin, and it was several years before the same degree of accuracy was attained again. He used plates from the 48-inch Palomar Schmidt and an average of ten comparison stars whose positions were well determined in each of forty-two fields. The standard stars were chosen from the best catalogues then available, namely the Yale Zone catalogue and the AGK2, and the effects of proper motion were ignored. To achieve the desired accuracy of less than 0.5 arc s r.m.s. in the optical positions of star-like objects fainter than 18 magnitude there are three chief requirements: first, an adequate plate scale of, say, 60 arc s mm⁻¹ or better; second, good images of the reference stars, which will probably be brighter than 12 magnitude, and the quasar, which may be fainter than 18 magnitude; and, third, a wide field of at least one degree to yield a good sample of comparison stars.

Unfortunately, there are only a few instruments, such as the 48-inch Schmidt, which have these qualities. This situation is likely to be somewhat alleviated in the near future, because two new large Schmidt telescopes (one at the European Southern Observatory in Chile and one at Siding Spring in Australia) should become operational later this year (see *Nature*, **239**, 489; 1972). But even with these new instruments the total load will be too great for the available wide-field instruments. The Isaac Newton Telescope, for example, has all the desired qualities at the prime focus except that the field of three-quarters of a degree is often too small to find enough comparison stars from the AGK3. It becomes necessary to use another telescope with a larger field to set up a secondary sequence of standards. There will clearly be difficulties encountered with unknown errors caused by the large ranges in magnitude and colour of the objects measured.

Nowadays it is customary to use lists prepared by a computer of stars within one degree of the quasar, taken from the AGK3 or the Smithsonian Astrophysical Observatory catalogue, and to apply proper motions to bring the star places to the epoch of the photographic plate. The reduction of the star measures made on digitized measuring machines is also computerized, using well-known equations for the plate reduction and the method of least squares.

The rapid progress of radio interferometry, notably by Sir Martin Ryle and the group at Cambridge, has increased the accuracy of radio positions until they equal or better their optical counterparts. One important question arises—does the optical and radio emission of small-diameter sources come from the same position in the sky? The affirmative answer is implicit in the work of Sandage, Kristian and Wade (*Astrophys. J.*, **162**, 399; 1970) although a counter example may have been found by Gent *et al.*

The increased accuracy of the radio interferometers has introduced a new aspect into the derivation of a fundamental system for star positions which was not envisaged a few years ago. Optical astronomers have been interested for a long time in using the galaxies as a fundamental reference frame without realizing that one day they could use the small faint point sources of quasars. In

fact radio interferometers give absolute positions and it is imperative to provide a frame of reference for calibrating radio against optical positions. The most important step in this direction was made by Murray, Tucker and Clements (*Roy. Obs. Bull.*, No. 162, 215; 1971) when they attempted to refer their positions directly to the FK4 system by using observations of comparison stars made with the transit circle. As Fricke has pointed out, technically there is no longer any obstacle to the extension of the fundamental system from the brightest stars to faint quasistellar objects.—From a Correspondent.

Age and Cancer Incidence

THE factor correlated most strongly with the rate of cancer incidence in humans is undoubtedly age; the probability that a man will develop a cancer in the next five years is 1 in 14 if he is 65, but only 1 in 700 if he is 25 (figures for Birmingham (UK), from *Cancer Incidence in Five Continents*, UICC, 1970). This represents a relative risk of about 50 to 1, and similar orders are found in many different animal species if the total rates of cancer incidence in late and early adult life are compared. In countries with adequate cancer registries, total cancer incidence can be separated into incidence rates for each organ of the body, and most of these separate rates increase between the ages of 25 and 65 approximately as the fourth or fifth power of age.

The process of transforming normal tissue into a pathological cancer can be shown to take place in several distinct "stages", each with its own causes. Many animal cancers, for example, are evoked only when a dose of an "initiator" is followed, perhaps months later, by a dose of a "promoter"; but not if these stimuli are given in the wrong order. Moreover, the incidence of human lung cancer is higher in ex-smokers than in non-smokers of the same age long after termination of smoking, which suggests that smoking acts on some earlier stage rather than the final stage of carcinogenesis.

If the kinetic rate-constants of the various stages of cancer are approximately independent of age, then in a five-stage system the rate at which cancers would arise in a large population of animals would be proportional to the fourth power of age. This means that the dependence of human and animal site-specific cancer rates on a power of age can be explained simply by assuming that a number of stages are involved and that no strong associations exist between age and the kinetic rate-constants of the various stages. Although it has been possible for decades to generate and study cancers in experimental animals, there is still little understanding of what these different stages may be.

Some stages may be specific mutations in cells in the target tissue, the occurrence of ageing processes in these cells, or they may be systemic, affecting equally all the organs in the body; if immunological elimination of pre-cancerous lesions is normal, for instance, then one or more of the stages may involve damage to this mechanism. There are two techniques which may prove capable of distinguishing between systemic stages and local stages, and of separating the effects of ageing from the mere accumulation of cells in the body which have already passed through the first stage(s). The effects of the same

carcinogen given at different ages can be studied; if a carcinogen can be found which elicits exactly the same response at all ages, then it will be possible to conclude that immunological changes and changes within the tissue caused by ageing are irrelevant. (Experiments to find such a carcinogen are now nearing completion.)

The other experimental technique is the transplantation of tissue from one animal to another, followed by chemical induction of cancer in the transplanted tissue. This has already been used to show that tissue from cancer-resistant or cancer-susceptible animals remains resistant or susceptible depending on the resistance of the host animal (Cowen, *Brit. J. Cancer*, **13**, 228; 1959). These experiments, however, related only to benign tumours and were not carried out in sufficient detail to exclude completely a relationship between the host and the eventual outcome; for this, it would have been necessary to have studied the fates of similar transplants in a variety of different animals. On page 280 of this issue of *Nature*, Ebbesen reports an experiment in which different transplants are given to similar hosts. He demonstrates that, unless an artefact has been produced in which sebaceous gland differences alter the effective dose of 7,12-dimethylbenz[α]-anthracene (DMBA), skin transplanted from old mice is more susceptible to carcinogenesis by DMBA than is skin transplanted from genetically similar young mice. This situation suggests that some at least of the increase in cancer incidence with old age is attributable to local changes in the target tissue.

Unfortunately, the effect that Ebbesen detects is much less marked than the expected effect of age on total cancer incidence. Moreover, the cancers evoked are benign rather than malignant, and the complementary experiments in which similar tissues are tested after transplantation into mice of different ages and in which DMBA is applied to untransplanted mice of different ages have not been carried out. But the technique of transplanting tissues of various ages into hosts of various ages is obviously very promising for determining the relevance (if any) of immunological or any other systemic changes in carcinogenesis.—R. P.

Electrons, Muons and QED

THE quantum theory of the electromagnetic field, quantum electrodynamics, now correctly predicts all relevant experimental phenomena over distances ranging from 2×10^{-15} cm out to 80 Earth radii, a span of more than 10^{20} , one of the greatest success stories in physics. The simplest possible system to study is the free electron, and for this the quantum fluctuations of the electromagnetic field close to the particle imply an apparent increase in its magnetic moment beyond the value of one Bohr magneton implied by the unmodified Dirac theory. So the gyromagnetic ratio (of magnetic moment to spin angular momentum in atomic units) is increased from 2 by the factor of 1.0011596527(24), the error on the last two digits being indicated in parentheses. This theoretical expression is known to 5 parts in 10^{10} from new calculations (Kinoshita and Critanovic, *Phys. Rev. Lett.*, **29**, 1534; 1972; Calmet and Peterman, to be published). To achieve such precision the theoretician must take into account a multitude

of rare fluctuations, which create ephemerally around the electron a variable swarm of accompanying photons and electron-positron pairs. Fortunately they can all be specified in terms of the Feynman rules, but nevertheless in several laboratories many man-years have been devoted to the problem.

The predicted value depends, of course, on the strength of the electron's coupling to the electromagnetic field as specified by the value of the fine structure constant α , which is known to 1.9 parts per million. This contributes an uncertainty of 22 parts in 10^{10} to the gyromagnetic ratio g , and is the chief ingredient of the error already quoted.

Experimentally the magnetic moment of the electron can be measured by studying its precession at rest in a magnetic field, but as the Bohr magneton itself is not known to much better than 1 part per million this would not lead to an accurate value for the g factor. It is possible, however, to measure directly the value of $(g-2)$; that is, experiments can be arranged which are directly sensitive only to the small correction occasioned by the quantum fluctuations. If a polarized electron is projected into a magnetic field so that it describes many almost circular orbits, then for $g=2$ it can be shown that the angle between its spin and its momentum must remain rigorously constant. So even after many turns the direction of polarization (relative to the direction of motion) would be the same. As g is in fact greater than 2 the polarization slowly changes: by measuring the spin-momentum angle as a function of time the value of $(g-2)$ can be determined directly.

In a twenty-year programme Crane and his colleagues at Ann Arbor, Michigan, have gradually refined the measurement of the electron "gyromagnetic anomaly", the current result being $g=2 \times 1.0011596567(35)$, in excellent agreement with theory (Wesley and Rich, *Phys. Rev.*, **A4**, 134; 1971; Granger and Ford, *Phys. Rev. Lett.*, **28**, 1479; 1972). The anomaly is checked to ± 4 parts per million, thus giving a remarkable confirmation of the theory and the procedures of quantum electrodynamics. Alternatively, if one believes the theory, the result can be interpreted as an independent measurement of α to an accuracy of 3 parts per million, adding significantly to existing knowledge based on other methods. If the accuracy could be further improved the electron gyromagnetic anomaly could give the most accurate, and certainly the cleanest, measurement of the fine structure constant. Nothing prevents this in principle, but who will undertake the painstaking effort involved?

An even better test of the theory is offered by the muon, which behaves exactly like an electron although it is 206.768 times heavier. It also has a gyromagnetic ratio of 2 plus a small correction: but because of the higher mass the quantum fluctuations involve energies 200 times higher and, in particular, evanescent electron pairs are created more frequently. Indeed, pairs of pions and other strongly interacting particles are present, often to a sufficient extent to contribute to the g factor. For the muon, also, a $(g-2)$ experiment is possible and has been carried out at CERN (Bailey *et al.*, *Nuovo Cimento*, **9A**, 369; 1972); this gives $g=2 \times 1.00116616(31)$, compared with the theoretical value (Lautrup, Peterman and de Rafael, *Phys. Rep.*, **3C**, 193; 1972) of $g=2 \times 1.00116588$. The agreement to 240 ± 270 parts per million in the anomaly is less accurate than for the electron, but because of the higher mass of the muon it has provided one of the

best tests of quantum electrodynamics at small distances (high energy), where departures from the theory (if any) are most likely to show up. This practically guarantees that the theory for the electron is good enough for a precise measurement of α to be trusted.

A new muon ($g-2$) apparatus is now being prepared at CERN. It involves a ring magnet 14 m in diameter in which the muon will turn thousands of times, and should give g to about 1 part in 10^8 . At this level quantum fluctuations involving heavy particles will be seen clearly, and may well lead to some surprises. Nobody can be sure that the effect of strong interactions between these particles has been estimated correctly, and of course undiscovered particles have not been taken into account, although obviously the muon itself may be aware of them. In particular somewhere, some day, one expects to find out why the muon is so heavy. If this can be attributed to a private particle coupled only to the muon, it could show up as a correction to the g factor.

—From a Correspondent.

ENERGETICS

What Price a Weasel?

from a Correspondent

LONG, thin mammals like weasels need more energy to run than do compact mammals like rats, according to James H. Brown and Robert C. Lasiewski (*Ecology*, **53**, 939; 1972). By comparing metabolic rates of weasels (*Mustela frenata*) with wood rats of the same weight (*Neotoma* spp.) at various temperatures, they found a 50–100 per cent increase in the metabolism of weasels. Three factors seem to govern this difference—the surface area of weasels is greater in proportion to the mass of the body than it is in the wood rat; their fur is less than half as long as that of the wood rat and has a correspondingly lower insulative quality, and, third, weasels are unable to attain a spherical or near spherical resting posture. Combined, these factors make the cost of thermoregulation rather high for the weasel as so much energy is dissipated as heat.

The high cost of thermoregulation, however, must have been offset during evolution by the advantages of a long thin body able to penetrate small cracks and burrows in pursuit of prey. The fact that many species of weasels and their relatives inhabit northern temperate, sub-arctic and even arctic regions is proof of their ecological fitness. Brown and Lasiewski suggest

that energetic efficiency has been sacrificed for enhanced predatory ability and, presumably, efficiency. A correspondingly greater amount of predation is necessary to support the energetically inefficient body shape. The application of Bergmann's rule, that animals evolve more compact shapes in cold climates to protect against undue heat loss, does not seem therefore to apply to weasels.

Brown and Lasiewski hit on a most interesting ecological point when they discuss sexual dimorphism of weasels. Males are significantly larger than females and may weigh up to twice as much. Ecologically this means that male and female weasels occupy virtually different feeding niches. Small fissures and burrows and the prey within them are exploited by the females, and larger crevices and the like are exploited by the male. Thus intersexual liaison benefits the species in that a territory is more fully exploited, as if by two species. Intrasexual competition, necessary for the maintenance of spacing patterns and population stability, is enhanced because of the weasels' increased energy requirement. The spread into a second niche through the agency of sexual dimorphism is not unique in the animal kingdom; in some deep sea fishes it is normal for the male to be parasitic upon the female. (Not only does this make the union of male with female easier, but it has important economic advantages in energetically impoverished environments.) The impact of *M. frenata* on the environment is essentially like that of two separate species.

Among the Mustelidae only those species with an elongate body form show marked sexual dimorphism. Obviously the elongate form and the sexual dimorphism evolved together, and now are totally dependent upon

one another. It seems that only by evolving into a secondary, sex specific niche by means of sexual dimorphism, can sufficient energy be harvested to allow the energetically inefficient body shape to function as a more efficient predatory machine. This has the effect of increasing the rate of energy flow in the environment—a useful feature in regions of intrinsically slow turnover—and of increasing the number of filled ecological niches without requiring the introduction of additional species. Bergmann's rule, if it applied in this instance, would be prejudicial to the development of the community, and to the expression of maximum ecological vitality.

TRANSFER RNA

Through Fields of Clover

from our Molecular Biology Correspondent

WHETHER it is a good idea for physical chemists to seek to bend the bow of the crystallographers by the pursuit of structural information about biological molecules is no doubt a matter of opinion. It is safe to say, however, that protein models based on ultraviolet difference spectra, optical rotation and the like have not proved the most enduring monuments of modern science. In the RNA field the prospects of extracting relatively hard, if modest, information, such as the degree and composition of base pairing, have seemed altogether more propitious, and much effort, more some might feel than the objectives justify, has gone into the development of methods to do just this, and to apply them to species of known sequence, particularly the tRNAs. The answers have in general been compatible with the pairing schemes imposed by the celebrated cloverleaf structure, and

Correlating Genetic and Translational Maps

IN *Nature New Biology* next Wednesday (January 31) Celis, Smith and Brenner report a set of those experiments in which molecular geneticists display their sophistication. Celis *et al.* have correlated the translational map and the genetic map of gene 23 of phage T4 (this phage has long been one of the happiest hunting grounds of molecular geneticists) and they find that for at least 40 per cent of this gene 0.012 recombination units of the genetic map correspond to one amino-acid residue in the gene 23 protein.

Gene 23 of phage T4 specifies a major polypeptide of the head of this phage. Furthermore, it has been shown that the polypeptide in the phage arises from the primary product of translation of gene 23 messenger from which an N-terminal fragment is cleaved. To com-

pare genetic and translational maps of gene 23, Celis *et al.* measured the molecular weights and characterized by fingerprinting the fragments of gene 23 precursor protein specified by a set of amber mutants which had previously been genetically mapped. A plot of the molecular weights of the fragments of polypeptide against the recombination distances between these amber mutants yields a straight line, the slope of which is 0.012 recombination units per 100 daltons of polypeptide, in other words per amino-acid. In spite of one anomaly—the polypeptide specified by a mutant E161 is about a third smaller than predicted—Celis *et al.* believe they may have hit on a constant physical unit of recombination. Further studies of other genes should decide whether or not this is the case.

this is also the case with the latest, and undeniably most elegant, and very likely most precise approach yet, which involves the use of high-resolution proton magnetic resonance in water solution. The results, as readers at least of the *New York Times* will know, will all too soon be subject to the most searching of tests, for the heavy tread of the crystallographers is already shaking the tRNA field.

What Wong, Kearns, Reid and Shulman (*J. Mol. Biol.*, **72**, 725; 1972) have done is to look at the resonances from the exchangeable protons of yeast phenylalanine tRNA. For this purpose it is necessary to work in water, for in deuterium oxide these protons exchange out and their signals vanish, so that, as Wong *et al.* point out, the best structural information is thrown away. The difficulties of operating near an immense solvent signal must be considerable, but the interesting regions are far enough downfield to make the operation possible. Wong *et al.* divide their spectra, done at 220 MHz on 5 per cent solutions of RNA into three regions. In the first, which extends from -6 to -9 p.p.m., one observes non-exchangeable base protons, and the exchangeable protons of amino-groups in both paired and unpaired bases. In D_2O only the first group remains, and their contribution can thus be determined and subtracted from the spectrum in water. There are two broad peaks, one centred at about -8 p.p.m., the other nearer to -6.5 p.p.m., and on the grounds of their relative positions, and the emergence of the second peak only at pHs appreciably below neutrality, where exchange with water is not too rapid, they are assigned respectively to paired and unpaired bases. The total numbers of protons contributing to the intensity of these two peaks are 67 and 45 per molecule, whereas that of the unexchangeable protons is 89 ± 4 , which agrees with the count of 89 from the base composition.

The least equivocal results on the extent of base pairing come, however, from a set of resonances lying between about -11 and -15 p.p.m. which on the grounds of earlier work on model systems can be assigned to internally hydrogen-bonded ring NH protons, each base pair contributing one such (because one ring NH only, in U or G, is implicated in each Watson-Crick pair). The A·U and G·C contributions are separable, especially in one spectrum obtained with a new 300 MHz instrument, which resolves nine peaks in this region, and seven A·U and eleven G·C pairs are deduced to be present. The cloverleaf scheme gives eight and twelve, as well as one putative G·U pair, so that this model, so far as it goes, is upheld by the results.

The figure of twenty base pairs deter-

mines the interpretation of the intensities of the exchangeable amino-proton peaks: each amino-group involved in base pairing must contribute both of its protons to the slowly exchanging category. With two amino-groups per G·C pair and one per A·U, the total comes to sixty-four, which agrees with the experimental value of sixty-seven. This behaviour is also required by the tritium exchange results of Englander and his colleagues, and this strongly reinforces the interpretation. There is also a small group of resonances in a third region (-9 to -11 p.p.m.), the intensity amounting to 4 or 5 protons, which may perhaps arise from features of tertiary folding.

In an accompanying article (*ibid.*, 741) the same authors give the results of a similar study of the ribosomal 5S species, and come up with twenty-one base pairs in the absence of magnesium, and twenty-eight in the presumed "native" state, when magnesium is present. Some 85 per cent of the base pairs are found to be G·C. This, if taken at face value, is enough to rule out most of the models of 5S RNA that have been proposed. Wong *et al.* infer from the rather low degree of pairing that the structure is rather open, and support this view by demonstrating a higher susceptibility to T_1 ribonuclease than that of tRNA. In this connexion a salutary note of caution comes from Mirzabekov and Griffin (*ibid.*, 633), who have used T_1 digestion and nucleotide mapping to look for the labile points in the 5S RNA sequence, which are presumed to be in single stranded loops. Taking care to maintain the magnesium-dependent native conformation throughout, they find that one scission occurs between residues 61 and 62. This evidently allows the excision of residues 57 to 61, which are missing in one of the fragments. Two further regions of attack are between residues 16 and 17, and 18 and 19 at the 5' end of the chain, and between 102 and 103 near the 3' end (the total length being 120 nucleotides). The corresponding placement of loops seems again to rule out some feasible pairing schemes. What is most striking, however, is that the results differ from those of Jordan, who found, in equally definitive terms, a break between residues 41 and 42. This lends substance to the notion that the molecule may enter a number of energetically almost degenerate structures, the stability zones of which are not easily defined.

FRESHWATER FISHES

Keys to British Forms

from a Correspondent

THE basic problem facing most biologists at some time or another is the



Typical scales from two contrasting British species of freshwater fish: above, cycloid type from the whitefish, *Coregonus lavaretus*; below, ctenoid type from the perch, *Perca fluviatilis* (plate taken from P. S. Maitland's new key).

correct identification of the forms with which they are concerned. Those working on aquatic animals in the British Isles have been helped in the past by the scientific publications of the Freshwater Biological Association. The most recent in the series is *A Key to the Freshwater Fishes of the British Isles with Notes on their Distribution and Ecology*, by Peter S. Maitland (*Sci. Publ.*, No. 27, 139 pp.; 1972). In a sense this publication breaks new ground, for it deals with a vertebrate group which is well known, for which the literature is easily available and in which the animals are relatively easily identified. Moreover, several recent books on the market cover the same ground. The publication is, however, more than a plain key to British freshwater fishes. It contains, besides the chief keys to families and species, preliminary keys to fish eggs, larvae, and scales. Furthermore, it includes maps of the distribution of the fifty-five freshwater or euryhaline species found in the British Isles.

These distribution maps bulk large at one per page in a publication of 139 pages. Nevertheless they provide valuable information in that they represent the results of a national scheme to collect data on the distribution of freshwater fishes. In 1969 Maitland (*J. Fish Biol.*, **1**, 45) outlined this scheme which was commenced a year or two earlier,

and was later prosecuted by the Biological Records Centre of the Nature Conservancy. It seems most remarkable that this is the first systematic attempt to map the distribution of freshwater fishes in the British Isles. Earlier statements of their distribution were apparently generalizations, based on reports in literature or museum collections, of presence or absence in river systems. Maitland's work on the mapping of observed occurrences is therefore a welcome addition to basic data.

Records of occurrence are shown by the standard 10 km square grid used by the Biological Records Centre. Like all distribution maps, they are open to the comment always made of such projects—that they show the distribution of recording observers rather than the animals concerned. Although this is true to some extent, it is equally true that this first printing should act as a spur to laggardly recorders, and generate a need for updating and re-printing soon. One hopes that future editions of the maps will be available at a more realistic price than the £1.20 at present charged for the whole publication.

The identification keys are presented in the classical manner with couplets which use several, chiefly meristic, characters at each step. This results in the usual cumbersome arrangement in which no short cuts are permissible, and one mistake can lead to disaster; the student simply has to plough through all the appropriate couplets with the thought that there must be an easier way to identify a fish than counting scales, fin rays, myomeres, gill rakers and so forth. To take an example, to identify a flatfish from a British river, one needs to work through five couplets (out of twenty in the family key) to get to the family (Pleuronectidae) and a page reference, on which one discovers that there is only one species anyway—the flounder.

The example begs the question, why in a key which is presumed to be used in the field or by the beginner in fish taxonomy is it necessary to follow slavishly a systematic order, and to overload each couplet with detail? The flounder, being the only flatfish, could have been dismissed in a single line on the first page to the great benefit of the user and a considerable economy of paper and effort.

The practical result of such a classical method and prolixity will be despair in most cases, and the user forced to look for the "best fit" illustration. Keys intended for use in identification (as opposed to those concocted to show systematic positions, or the ingenuity of the compiler) should be simple and unambiguous, using characters which are, if not trenchant, then easy to assess. The only justification that can be offered

for the present style is that a worker totally unfamiliar with the subject could use the key, but even the simplest student is likely to wonder at the choice offered in several couplets, as "Less than 13 rays in the anal fin . . ." versus "More than 11 rays in the anal fin . . .". There must be easier ways of identifying fish than this.

TRANSFORMATION

Genomic Parameters

from our Cell Biology Correspondent

ESTIMATES of the number of genomic equivalents of simian virus 40 DNA in cultured cells transformed by SV40 are markedly dependent upon the methods used to measure the amount of SV40 DNA in a known amount of cellular DNA. Westphal and Dulbecco, who developed a method for transcribing *in vitro* with *Escherichia coli* RNA polymerase SV40 DNA and then hybridized this labelled virus-specific RNA to transformed and untransformed cell DNA stuck to nitrocellulose filters, have estimated that cells of a particular line of SV3T3 transformants contained forty-four genomic equivalents of SV40 DNA. But when Gelb *et al.* estimated this parameter from measurements of the rate of reannealing of SV40 DNA in the presence of DNA from these SV3T3 cells and in the presence of untransformed 3T3 cells they came up with the value of 1.42

SV40 genomes per cell. Even allowing for the different values assumed by these groups for the weight of the 3T3 cell genome there remains a twenty-fold discrepancy.

It is nowadays generally accepted that the estimate of Gelb *et al.* is the more accurate, not least because, as Haas, Vogt and Dulbecco showed recently, DNA hybridized to RNA tends to come free from nitrocellulose filters, and, no doubt for the same reasons, Pettersson and Sambrook's estimate (*J. Mol. Biol.*, 73, 125; 1973) that rat cells transformed by adenovirus 2 contain about one genomic equivalent of adenovirus 2 DNA per diploid amount of cell DNA is closer to reality than the estimates of fourteen to thirty-seven genomic equivalents of adenovirus 2 DNA per cell genome reported in 1970 by Green and his colleagues, who used the RNA/DNA hybridization technique. The transformed rat cells used by Pettersson and Sambrook were separate stocks, originally derived from the same transformant grown from many cell generations in different laboratories. Clearly the amount of adenovirus DNA in such cells is stable. Furthermore, because the transformed rat cells are aneuploid it is currently difficult to calculate just how many viral genomes there are in each transformed cell genome as opposed to per diploid amount of cell DNA, but the number must be very small.

Like adenovirus 2, adenovirus 12 transforms rodent cells, and according

Taxonomy of RD114 Virus Particles

RD114 VIRUS is a C-type RNA virus liberated from a line of human tumour cells which was passaged in kittens. Because of the history of these human cells which liberate RD114 virus two possible origins of the virus have to be considered; it might be a feline virus picked up during the passage in kittens or it might be a human virus, related to the RNA tumour viruses of lower mammals, the replication of which was induced when the human cells were passaged in kittens. A variety of serological tests have shown that RD114 virus particles are not antigenically related to known feline C-type viruses, and in *Nature New Biology* next Wednesday (January 31) Huebner's group (Long *et al.*) report experiments which they believe "add to the indication that RD114 is most probably a human virus".

Long *et al.* inoculated partially purified RD114 virus particles into guinea-pigs and obtained from these immunized animals antisera which strongly inhibit the reverse transcriptase activity present in RD114 virions. They then

assayed these antisera for their ability to inhibit the reverse transcriptase activities present in primate, feline, murine, avian and viper C-type RNA viruses. It has, of course, been shown repeatedly that the reverse transcriptases present in these different groups of viruses are antigenically distinct and that transcriptase inhibition tests using antiviral antisera indicate taxonomic relationships between these viruses.

Long *et al.* find that antisera to RD114 virions reproducibly and completely inhibit the reverse transcriptase in this virus and also inhibit to a significant extent the transcriptase activities in two primate C-type viruses. The anti-RD114 antisera do not, however, reproducibly inhibit the enzymes in feline, murine, avian and viper viruses. Clearly this result is compatible with the idea that RD114 is a human C-type virus, but it is surprising that Long *et al.* did not carry out the reciprocal tests, challenging RD114 particles with antisera against the two primate viruses; these tests should be done, for they may clinch the case.

to Champe, Strohl and Schlesinger (*Virology*, **50**, 482; 1972) tumour cells induced in hamsters by injections of adenovirus 12 contain a factor, resistant to digestion by nucleases but sensitive to pronase, that reduces by up to 99 per cent the yield of adenovirus 12 made in permissive cells infected by this virus. Champe *et al.* claim that this inhibitory factor decreases the rate of replication of adenovirus 12 in permissive human embryonic kidney cells as well as the final yield of virus from each cell and that it does not inactivate purified infectious viruses. This fact, and the observation that the factor does not inhibit T antigen synthesis in infected cells, leads them to conclude that the factor is more likely to inhibit some late events in adenovirus 12 replication than the adsorption, penetration and uncoating of the virus. The factor is virus specific and therefore not likely to be an interferon, but so far Champe *et al.* have no real idea as to its target.

Reznikoff, Tegtmeier, Dohan and Enders (*Proc. Soc. Exp. Biol. Med.*, **141**, 740; 1972) have addressed themselves to a superficially at least not dissimilar problem, namely the identification of the resistance of certain AGMK cells to SV40. Most AGMK cells are fully permissive for SV40 and are killed by the virus as it replicates, but some AGMK cells become chronically infected rather than lytically infected and may even be transformed by SV40. Reznikoff *et al.* have investigated the effects of SV40 specific antiserum on such chronically infected AGMK cells. In the presence of this antiserum clones of chronically infected cells can be cured of all detectable traces of SV40 virus and its antigens, and at least one cured clone of cells cannot be infected by SV40 virions but can be infected and killed by naked SV40 DNA.

One simple interpretation of these data is that part of the resistance of these cells to SV40 stems from some block before the uncoating of the viral DNA, but there is almost certainly more to the story than that, not least because an absolute block to virus penetration and uncoating would obviously preclude the emergence of SV40 transformed AGMK cells.

SOLID STATE

More on Ferrofluids

THE properties of ferrofluids—liquids like mercury containing small particles of a ferromagnetic substance—have been further examined by Shepherd, Popplewell and Charles of the University College of North Wales, and their results are published in a recent issue of *J. Phys. D.* (**5**, 2273; 1972). Ferrofluids are of particular potential importance

because they can be used as an efficient means of energy conversion; if part of a ferrofluid contained in a toroid is placed in a magnetic field and heated to the appropriate Curie temperature the whole fluid will move. It turns out that the power that can be generated in this way per unit mass of fluid depends on the square of the change in magnetization with temperature (dM/dT) and on several other parameters such as the Curie temperature.

Shepherd and his colleagues have made ferrofluids containing particles of iron-nickel alloys of various compositions. In most cases the largest of the particles were of order 1,000 Å, and the concentrations were 1 to 2 per cent by weight. Their method of making the ferrofluid is electrolytic, and utilizes a mercury cathode and an electrolyte of ferrous nickel ammonium citrate of the appropriate composition for the alloy required. Magnetic measurements on several Fe-Ni ferrofluids at 77 K showed that the coercive force for a fluid of a given particle concentration and composition passes through a maximum as the current density used in the electrolytic cell is increased. Shepherd *et al.* conclude, however, that the maximum is not attributable to an increase in particle size such that the particles contain more than a single domain; rather, it is a consequence of variations of size and

shape in an essentially single-domain region.

COMPUTERS

On-line in the Lab

from a Correspondent

COMPUTERS, it need hardly be said, are, or ought to be, the experimenter's best friends, for they collect data, work out results, and, better still, run apparatus. Nevertheless, how to choose a computer, how to link it to an experiment and how to use it to best advantage remain questions to which answers are far from obvious. Faced with such problems the research worker will benefit from the experiences of other scientists who have taken the plunge and are now engaged in computer-linked experimentation.

Such a communication exercise between current users and prospective users of laboratory computers was the chief purpose of a conference organized by the Electronics and Computational Physics groups of the Institute of Physics and held on January 3 at Imperial College, London.

The special features of the conference included an audience which, although non-expert as far as computer applications are concerned, consisted of trained scientists; contributions solely from "users", thereby excluding parties

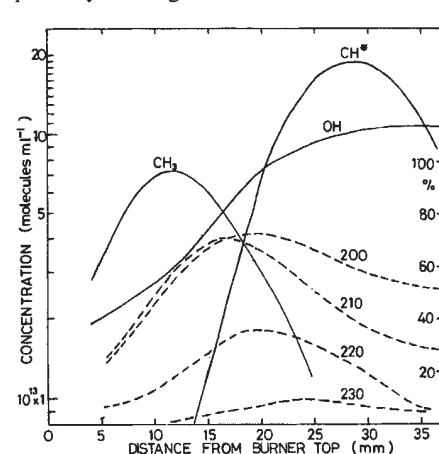
Methyl Radicals in Flames

RELATIVELY little is known of the exact way in which methane flames burn, except that methyl radicals are involved. Their concentration, however, is known in only the most approximate terms, chiefly because of the difficulties of applying mass spectrometry to the problem.

In 1960, Gaydon *et al.* (*Proc. Roy. Soc.*, **A256**, 323) first used absorption spectroscopy to detect the ultraviolet absorption of methyl radicals at 216 nm and to calculate at least an upper limit to the methyl radical concentration. In next Monday's *Nature Physical Science* (January 29) Harvey and Jessen report that they have used improved absorption techniques to detect strong absorption at 216 nm in several types of flame. They burned methane, ethane, propane, ethylene and acetylene at pressures of about 4 torr and gas flow rates of about 10 l. min⁻¹.

In order to make the study of the distribution of the methyl radical concentration within the flames more simple, Harvey and Jessen diluted the flow of hydrocarbon and oxygen with 3 l. min⁻¹ nitrogen. What they found is shown in the diagram. It also turned out that there is another absorption feature at 212.5 nm in the flame spec-

trum; this is presumably part of the methyl spectrum. Unexpectedly, Harvey and Jessen find that the methyl radical concentrations are roughly the same (1 in 10³ to 10⁴) in the other hydrocarbon flames examined. In acetylene, for example, they say that their results are consistent with the occurrence of the reaction $C_2H_2 + OH \rightarrow CH_3 + CO$ possibly among others.



—, Concentration of CH_3 and OH and intensity of CH emission at 430 nm (arbitrary units); ---, variation of continuous absorption at various wavelengths (nm).

with some possible self-interest, such as manufacturers of equipment; and the division of the meeting into two distinct activities, namely, a survey session, with three contributions, intended to set the current scene, and a series of "case studies"—short contributions in which successful applications of on-line methods in a variety of disciplines were presented.

In a comprehensive review of the present range and facilities of mini-computers—defined as machines possessing input/output channels and "interrupt" (externally initiated program branching) capabilities—D. Turtle (Electrical Research Association) drew attention to the future potentialities of the range of microprocessors which may, before long, provide special purpose systems at a cost of around £1,000 or less by contrast with the present costs of small computer systems which run, typically, from around £8,000 for a machine with two registers, an eight-bit word, and sixteen input/output channels to perhaps £30,000 for one with sixteen registers, a twenty-four-bit word, and 256 input/output channels.

With the universal use of large-scale integrated circuits and the introduction of new, fast and cheap semiconductor random access and read only memories the possibilities for further reductions in cost and increases in systems capability are by no means exhausted. At one end of the spectrum the system of the future will be characterized by an arrangement in which all component systems (central processor, input/output processors, special arithmetic units, fast and slow stores) will communicate directly with each other, so that many processes may be carried out simultaneously. At the other end, small microprocessors, specifically designed for each application and comprising a few integrated circuits on a single circuit board, will be powerful enough to exert a supervisory and controlling function for many types of experiments.

The problems of physical inter-connection of apparatus and computer, which were considered by J. M. Richards (Computer Analysts and Programmers), offer a choice of two solutions: direct interfacing to the computer's input/output channels for maximum data transfer rates, or use of an intermediate standard interface system. The universality of the latter approach, pioneered by the nuclear physicists and resulting in the internationally standardized CAMAC system, makes it attractive to anybody who can accept the small reduction in the rate of data transfer. One of the benefits of standard interface systems lies in the relative ease with which an experiment can be transferred from one computer to another.

Having successfully linked his apparatus to his computer the experimenter still has to write his program, for he will rarely be content to use a manufacturer's application package (even if he can afford it). By means of an elaborate flow chart E. G. Murphy (UKAEA) gave guidance about the many choices now open. Only a few years ago use of assembler language was virtually compulsory, but now alternative approaches have become available to the experimenter. The choice of a good operating system and a realistic assessment of the maximum data rates required are all-important in this area.

In the session of case studies C. Derrett (MRC Air Pollution Unit, London) presented an attractively simple approach to the use of an instrument-linked computer system by non-specialists, based on an extension of the well known and simple BASIC programming language to include peripheral handling routines by means of simple CALL statements. At the opposite end of the spectrum of complexity stood two contributions from UKAEA staff at Culham describing a large data acquisition system, and the monitoring and control of a fusion experiment.

The meeting, which attracted more than 200 participants, illustrated clearly that the day when some kind of computing apparatus will form part of almost every experiment is rapidly approaching. In the meantime there seem to be many scientists who, having become convinced on-line experimenters, are willing to let their experience help those who have yet to take the first step.

More About Cygnus X-3 Radio Flares

SINCE the great radio flares of Cygnus X-3 in September and October last year, radio astronomers have kept a watch on the source for more unusual events. These have not as yet materialized. But as a result of the quiescent state of Cyg X-3 since October, Lequeux *et al.* have been able to carry out absorption measurements at 21 cm which establish a reliable lower limit on the distance to the source. The same team carried out similar measurements during the flares; but the work described in next Monday's *Nature Physical Science* (January 29) provides the first proper base line for measurements of this kind, because the observed properties of Cyg X-3 during the flares can hardly be regarded as typical. From these measurements of the absorption between the Earth and Cyg X-3, it is clear that the source is at least 11 kpc away, although it is not clear whether it lies inside or beyond the spiral arm of our Galaxy

PLATE TECTONICS

Thickening Lithosphere?

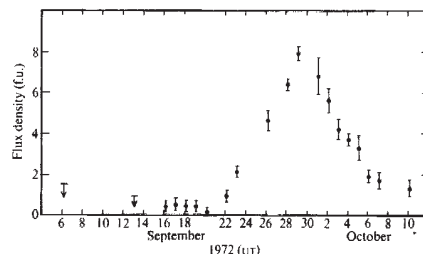
from our Geomagnetism Correspondent

WITH the publication of some new comments and calculations by Forristall (*J. Geophys. Res.*, 77, 6407; 1972), the search for the most plausible plate tectonic mechanism can be said to have taken another small step forward, although, as Forristall himself freely admits, some may feel it to be a step backwards, or at least sideways. This is not because he has returned to some mechanism now discredited by geophysicists; on the contrary, he supports the plausibility of the newest idea of all—active, as opposed to passive, lithospheric spreading. The problem is that the plausibility seems to require variability in the thickness of the oceanic lithosphere, an idea which Forristall feels is "certain to be controversial".

According to Forristall's definition, passive spreading is the old mechanism whereby the lithosphere is carried along by convection in the softer asthenosphere below. In this case the velocity in the asthenosphere must increase for some distance below the lithosphere-asthenosphere boundary in order to produce the shear stress necessary to move the lithosphere along. One problem with this is that the resulting high aspect ratio cell is unlikely to be stable; and yet convection extending into the lower mantle, although not entirely discredited, also has its problems. Active spreading, on the other hand, assumes the lithosphere itself to be the prime mover, the driving force being the gravitational forces at elevated ridges or, alternatively, at the descending litho-

which lies at about that distance in the same direction.

Also in next Monday's issue, Bash and Ghigo present observations of the historic flares themselves, at 365 MHz. These show the full extent of the second and larger flare, which lasted for more than two weeks (see diagram). More detailed observations have revealed a triple structure within this broad peak, which was also much greater in magnitude than the first event.



Second flare of Cygnus X-3. Observations at 365 MHz.

sphere. Either way, there must be a viscous drag from the asthenosphere which resists lithospheric motion.

On the face of it, active spreading seems unlikely, partly because the relatively thin lithosphere is required to transmit horizontal stresses over long distances and partly because of the difficulty in finding the force which produces the return flow in the asthenosphere. In addressing himself to the first of these problems Forristall notes McKenzie's point (*Geophys. J.*, **18**, 1; 1969) that tensile stresses are not required in the case where motion is caused by the descending lithosphere, but nevertheless uses them as a limiting condition in calculating the no-failure point in the lithospheric plate.

To be more specific, Forristall considers a model in which an elastic lithosphere, susceptible to failure according to the Mohr-Coulomb law, overlies a Newtonian asthenosphere. As the denser lithosphere descends into the less dense asthenosphere, the motion produces a relief of horizontal stress at the leading edge of the horizontal part of the plate and boundary stresses on the plate. What this stress relief means is that it is no longer valid to envisage the sinking plate pulling the rest of the lithosphere with it; it is the normal hydrostatic pressure at the trailing edge which pushes the plate towards the trench. Another consequence is that near the trench the horizontal principal stresses are lower than the vertical stresses.

In a series of stress calculations, Forristall then determines how great the stress relief can be without causing a failure in the plate. It turns out that, for horizontal stress relief at the leading edge of the horizontal part of the plate, the shear stress along the base of the lithosphere is constant. And because this shear stress arises from viscous drag, it can be related to the viscosity of the asthenosphere, given the vertical velocity gradient beneath the plate (actually calculated from the Navier-Stokes equation). What this means is that the no-failure condition for a lithosphere of any given thickness can be stated in terms of the maximum value of the asthenosphere's viscosity at any given asthenospheric thickness. Of course, the viscosity and thickness of the asthenosphere are not known with any certainty and so exact solutions are not possible. But by comparing his relationships with the viscosity and thickness values determined from the uplift of Fennoscandia (leaving aside the question of whether the behaviour of shield areas is really relevant to the suboceanic situation), Forristall concludes that to prevent lithospheric failure the asthenosphere must be less than 300 to 400 km thick; in other words, active spreading is only possible under this condition.

The problem of the driving force causing the return flow in the asthenosphere is less tractable and seems to require what really amounts to an *ad hoc* solution and at least one *ad hoc* rationalization. It is easy enough to calculate from Forristall's analysis the value of the required pressure gradient, but less easy to discern its physical nature. Forristall postulates that the lithosphere thickens towards the trench, producing a horizontal pressure gradient beneath it. But a thickening of the lithosphere implies an excess mass and hence a large positive gravity anomaly. The observed gravity anomalies at trenches are certainly not large enough for Forristall's purpose, which leads him to speculate further that the excess mass is compensated by a mass deficiency lower in the mantle. One possi-

bility here is that the asthenosphere extends to greater depths in trench regions.

As an example of the magnitudes involved, Forristall considers the lithospheric thickening necessary if the density contrast between the lithosphere and asthenosphere is 0.06 g cm^{-3} . If the thickness (x) of the lithosphere at the ridge is 20 km and the thickness (y) of the asthenosphere (assumed constant) is 200 km, the lithosphere must thicken to 180 km at the trench. For $x=50 \text{ km}$ and $y=200 \text{ km}$, the lithosphere must be 250 km thick at the trench. And if $x=20 \text{ km}$ and $y=150 \text{ km}$, the plate must thicken to 95 km. In other words, the required lithospheric thickening is far from trivial, although it is relatively smaller the thinner the asthenosphere.

Explaining the Spectra of Heavy Cosmic Rays

FOUR communications in next Monday's *Nature Physical Science* (January 29) discuss and supplement the evidence that there are relatively more heavy cosmic ray nuclei—iron for example—in the cosmic rays impinging on the Earth's atmosphere at energies of several tens of GeV per nucleon than at lower energies.

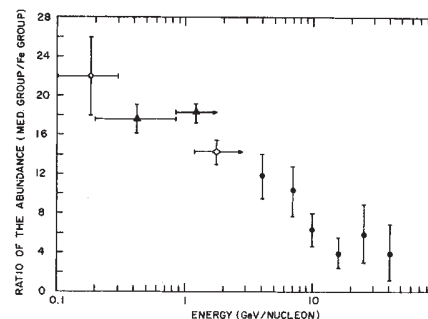
The situation is summarized in the diagram, which shows some of the data obtained by Ormes and Balasubrahmanyam as closed points. What they have done is to fly a balloon carrying detectors to measure particle charge and energy near the top of the atmosphere for 16 h. The remainder of their data comprise the differential spectra of several nuclei and groups of nuclei at energies greater than 3.3 GeV per nucleon. They conclude that the so-called secondary nuclei (that is those formed chiefly by the fragmentation of iron and nickel interacting with interstellar hydrogen) have somewhat steeper energy spectra than the cosmic ray "source" nuclei (chiefly iron and nickel). If these spectra continue to higher energies, say Ormes and Balasubrahmanyam, iron will become the most abundant nucleus apart from protons and helium nuclei at around 200 GeV per nucleon.

Although Ormes and Balasubrahmanyam draw some conclusions from their results, it is the other three groups of authors who delve deeply into the ramifications of the spectral differences between heavy and light nuclei for theories of the origin and acceleration of cosmic rays. Webber, Lezniak, Kish and Damele consider an equilibrium model for cosmic ray production and leakage from the Galaxy in which the "escape length" is assumed to be a function of energy. They find that a dependence of E^{-1} fits

the energy variations of both ratios $(C+O)/(Fe+Ni)$ and $(\text{Nuclei with } Z=17-25)/(Fe+Ni)$. On the other hand, such a strong dependence on E does not seem to be reflected by the ratio of the number of Li, Be and B nuclei (thought to be secondary nuclei) to the number of C and O nuclei (primary nuclei). The question of the energy dependence of the theoretical term which describes the probability that galactic rays leave the Galaxy is also considered by Audouze and Cesarsky.

In the final communication Mene-guzzi comes to the conclusion that the energy dependence of the abundance ratios is consistent with a decrease of the cosmic ray escape length from about 7 g cm^{-2} at about 2 GeV per nucleon to less than 1 g cm^{-2} at 100 GeV per nucleon. He rejects the need for additional assumptions like a dependence of the mean free path on charge or a charged dependence of the spectral index of the source.

As Audouze and Cesarsky point out, many of the data now available seem to upset the theories that require cosmic rays to be confined to the disk of the Galaxy.



Ratio of abundance of "medium" nuclei ($6 \leq Z \leq 9$) to those in the iron group ($23 \leq Z \leq 28$) as a function of energy per nucleon.

X-ray Star Problems Defined

by our Cosmology Correspondent

At a specialist meeting of the Royal Astronomical Society on January 12, problems raised by the discovery of X-ray sources in binary systems were placed in the perspective of the latest observations at radio, optical and X-ray wavelengths. Few detailed answers to these problems have yet emerged; but theoreticians are now learning which questions must be answered by the observations in order to differentiate between those models which are at present plausible.

The first speaker, Dr K. A. Pounds (University of Leicester), described some of these observations at X-ray frequencies—not, this time, the work of his own group, but chiefly the Uhuru observations. He reported that American Science and Engineering are now preparing the third Uhuru catalogue (3U) which will include some 200 sources, down to an intensity 10^{-3} times that of the Crab. It seems that these 200 sources are divided almost equally between galactic and extragalactic objects. Of the galactic sources, the binary systems which are arousing so much interest form a subset of six in our Galaxy and one in the Small Magellanic Cloud.

Several of these sources show a rapid variation with a period of a second or two (reminiscent of pulsars) superimposed on a binary period of hours or days. One of the most interesting results to emerge from extended observations during the past few months is that in some cases at least this rapid variation is speeding up. Her X-1, for example, has a "pulsar" period of 1.2 s and a binary period of 1.7 day; the former now seems to be increasing by 4 μ s in six months, according to recent MIT data which Dr Pounds reported.

Two of the sources have been studied in detail by optical astronomers. Dr P. Murdin (Royal Greenwich Observatory) described these studies of Her X-1 and Cyg X-1—which have received this concentrated attention, of course, simply because of the lack of reliable optical identifications of the other sources. Her X-1 has been identified with HZ Her, a 14 mag star which shows the same binary period of 1.7 day as the X-ray source. The primary in the system seems to be affected by the X-ray emission of the companion, but a reasonably comprehensive model has been proposed by Forman *et al.* (*Astrophys. J. Lett.*, 177, L103; 1972; see also *Nature Physical Science*, 240, 169; 1972). At X-ray frequencies, the source also shows a regular 35-day variation, which has yet to be explained, and there is marginal evidence for

optical variations at the "pulsar" period.

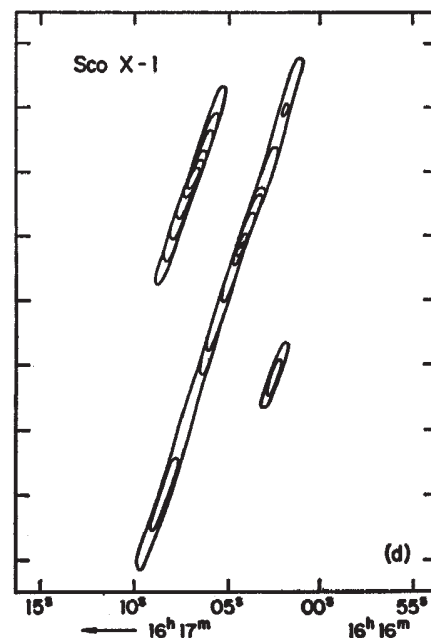
Cyg X-1, however, is the joker in the binary X-ray star pack. As Dr Murdin put it, this is "something completely different". This optical identification was achieved by a roundabout route, which verges on being a circular argument. Early last year, the emission of the source in different X-ray channels changed abruptly; at the same time, a new radio source appeared in that part of the sky, and the radio position is good enough to permit identification of the radio source with a BO supergiant. There is no direct reason to connect the X-ray source with either the star or radio source, but the coincidence of the sudden change in X-ray properties with the appearance of the radio source is so strong that nobody has seriously questioned the identification of Cyg X-1 with the BO supergiant. This is the source which many theorists have turned to as evidence that black holes exist. Dr Murdin stressed, however, that although the source is clearly unusual, and asymmetry in the light curve implies that the stars in the system are non-spherical, the optical data are consistent with the view that the secondary is an early main sequence star. There is no pressing need to invoke the "counsel of desperation" hypothesis that there is a black hole in the system. Black holes, he says, are a solution looking for a problem.

In discussing the radio properties of these objects, Dr G. K. Miley (Westerbork) concentrated chiefly on the remarkable outburst of Cyg X-3. Most of the work described has already appeared in *Nature* (see special issue of *Nature Physical Science*, October 23, 1972). But one interesting possibility which Dr Miley pointed to is that the triple radio source associated with Sco X-1 might have originated in an explosion similar to the event recently observed in Cyg X-3. Other than Cyg X-3 at the time of the two flares, all these binary X-ray systems are weak or non-existent radio sources; only Cyg X-1 and Cyg X-3 are firmly identified at radio frequencies, and, although Sco X-1 may be of the same family as Cyg X-3, no one consistent model will explain the observed properties of all three objects.

It was left to Professor Martin Rees (at present at the University of Sussex but shortly to return to Cambridge as Sir Fred Hoyle's successor as Plumian Professor) to discuss the theoretical problems—not, he was quick to point out, to provide the answers to the questions raised by the observations. It seems that the overall features are happily explained by a model in which

a giant star has a magnetic neutron star companion. Under those conditions, slight mass loss from the giant—even a strong stellar wind—can cause enough matter to accrete onto the neutron star to produce the observed X-rays, because as much as 10 per cent of the rest mass energy of the infalling matter is liberated as it falls down the neutron star's potential well. The mechanism is not unlike that of a pulsar in reverse, for pulsars are generally believed to be losing matter by outflow along lines of magnetic force. Professor Rees suggested that this could be why X-ray "pulsars" are seen in binary systems, where there is infalling matter, but radio pulsars are found only in isolation. Also, transfer of angular momentum by the infalling matter should cause the neutron star to spin faster, in agreement with the latest X-ray observations.

The detailed answers to the many problems raised at this meeting remain to be found. Why do the X-rays in these sources sometimes "switch off" for days at a time? Why do the optical variations show no similar behaviour? How did these binary systems evolve to their present state? Is there a black hole in Cygnus X-1? And in addition searches of survey plates show that the optical variations of Her X-1 sometimes switch off for years at a time. This raises the number of time scales associated with that source, at least, to four. But the problems are not insoluble; their number simply indicates the vigorous growth of this new branch of astronomy.



Sco X-1 mapped at 2,695 MHz (after Hjellming and Wade, *Astrophys. J. Lett.*, 164, L1; 1971). Could the triple structure—smeared in this figure by the antenna response—be the result of an outburst like that recently observed in Cyg X-3?

Is Polio a Model for Consumer Research?

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Dr Wyatt considers to what extent the customer-contractor principle was at work in research on poliomyelitis.

In the discussions of the Rothschild proposals for financing applied research, there has been little attempt so far to examine previous case histories to see if the formula has worked in the past. Nor has the relation of pure or basic to applied work been examined: if, as suggested by the research councils¹, much of their basic work is funded for its relevance to specific ends, then much of the controversy would seem pointless.

The control of poliomyelitis is a cautionary tale, successful though the outcome may have been. There were four clearly defined phases. From about 1880, when poliomyelitis was first recognized as a problem, until 1934, research was carried out by individuals financed from a variety of sources. The production of a book on poliomyelitis² marked the beginning of more deliberately directed effort. In 1934 a consumer-directed body, the President's Birthday Ball Commission, funded, among other work, applied work on a vaccine. The Commission was replaced in 1938 by the National Foundation, another consumer body, which worked through a scientific research committee in much the way Rothschild proposes. For ten years it funded pure research, for the next ten a mixture of pure and applied. How well, or how badly, did each of these systems work? And what lessons are to be learned about the control and funding of customer-directed research?

In medicine, and perhaps agriculture, practical problems must be tackled before the technical means of solving them are known. The principal cause of poliomyelitis, a virus, was discovered by Landsteiner and Popper³ in 1909 (although this was still disputed twenty years later). But the bases for all further work were clearly shown by Wickman⁴ in 1913: poliomyelitis is caused by a virus in the spinal cord, with inflammation of the motor ganglia, the disease can be reproduced in monkeys, the incubation period is probably more than 4 days, monkeys can acquire immunity (antibodies), it is an infectious disease spread by humans who show no overt disease (healthy carriers) or who have abortive attacks, insect vectors play no part in its transmission, and the virus could be recovered from the human intestinal tract. Historically, however, almost 40 years were needed before these ideas were accepted and even though immunity had been demonstrated in monkeys and the incidence of poliomyelitis was lower in adults than in children, thus suggesting the acquisition of natural immunity by human beings, the goal of a vaccine against poliomyelitis was delayed for several years. Why should there have been such a delay?

The concentration of research at one great centre, the Rockefeller Institute, was partly responsible, and the opinions of Flexner, its head, carried too much authority. As late as 1926 he and Noguchi were still claiming that a globoid body, growing in lifeless medium, was the causative agent of poliomyelitis. Concentration of research at the centre of excellence resulted in several technical errors which were not recognized until the 1950s. The MV strain of virus, which had been used at the Rockefeller, was then shown to be so adapted to monkey brain passage and so neurotropic that it would no longer

grow in cells from other organs. Thus in 1936 Sabin and Olitsky had failed to grow it in tissue cultures and this was accepted until 1949 when Enders, Weller and Robbins grew it in human non-nervous tissue. The MV strain was also probably an inconstant mixture of viruses of different types. Monkeys immunized with this mixed strain were sometimes found to be susceptible to further challenge. Although Burnet and Macnamara⁵ had presented evidence that there might be two antigenic types, the MV strain was still used. Also the MV strain would not infect cynomolgous monkeys by feeding.

The factors so clearly deduced by Wickman⁴ from the natural disease in man were tested in the 1930s, but were obscured by the results obtained from tests involving animal models. The solution of the technical problems of infecting monkeys introduced new—and on the whole, irrelevant—ideas. One such was the theory of infection by way of the olfactory nerves, originally put forward by Flexner in 1910. Monkeys could be infected by rubbing poliovirus into the nasal mucous membrane, but this was an artificial route. It led, however, to the attempt in 1936–38 to block virus entry of children by treatment of the mucous membranes of the nose with chemicals. This was probably ineffective, was impracticable and could result in the loss of sense of smell.

On the other hand, the Rockefeller Institute, as a centre of excellence, attracted many who afterwards made such significant contributions: Herald Cox, Isabel Morgan, Sabin and Syverton all worked with Olitsky. The institute was also the home of Rivers, who later presided over the funds for polio research.

Funds for Research

In 1934 a new body, the President's Birthday Ball Commission, began to give funds for research through a scientific advisory committee. This corresponded to a consumer body: it comprised a neurosurgeon, a third vice-president of the Metropolitan Life Assurance, the director of the Hygienic Laboratory of the US Public Health Service (forerunner of the National Institutes of Health) and Dr Paul de Kruif, a microbiologist turned writer. It was not strong on science and gave most of its funds (\$241,000 in 1935) for applied work on the production of a vaccine⁶. The Park-Brodie formalin vaccine was ineffective at best, and the Kolmer vaccine, a so-called attenuated vaccine, caused at least five deaths⁷. The first attempts at applied science had ended in failure because there was no sure basis of knowledge on which to rest them. But, surprisingly, the Rockefeller Institute, which had not been involved, rapidly faded from the poliomyelitis field. Whereas much of the previous work had been done in public health laboratories, the emphasis now shifted more and more to the laboratories of the medical schools. The United States government remained conspicuously absent and seemingly only intervened when things went wrong—Dr Leake, a USPHS officer after the Kolmer and Brodie incidents and the USPHS after the Cutter incident in 1955 (ref. 7).

Success of a Rothschild-type Body

In 1938 the Ball Commission was replaced by the National Foundation for Infantile Paralysis. The composition of the scientific research committee, with Tom Rivers as chairman, was less consumer-oriented and was more like that of a

research council: one lay member, one government administrator/scientist, three top virologists (including Rivers) and an ex-scientist (de Kruif) as secretary. An eleven point programme⁶ was adopted, in order of importance: pathology of poliomyelitis in human beings; portal of entry and exit of virus; purification and concentration of virus; what is to be called poliomyelitis?; mode of transmission of virus from man to man; transmission of virus along nerves; further attempts to establish poliomyelitis in small laboratory animals; settlement of the question of chemical blockade; chemotherapy of poliomyelitis; relation of constitution to susceptibility; production of a good vaccine. Basic science was clearly placed first, with prevention of the disease when possible.

From the outset, the National Foundation, guided by Rivers and his committee, funded work not only on poliovirus but on many other viruses and even on bacteriophage and protein chemistry (Linus Pauling). It also funded general fellowships for work and travel (J. D. Watson). The foundation also gave very large sums of money for what might now be considered wasteful duplication of work: at least three large groups on the epidemiology of poliomyelitis and the continued funding of Sabin for the work leading to his oral vaccine when the foundation was heavily committed to Salk and his inactivated vaccine.

It was Dr Maxcy, an academic, who approached the foundation for a five year grant to fund a permanent research centre at Johns Hopkins School of Hygiene to investigate the pathology and epidemiology of poliomyelitis. This led to a new concept of funding—later adopted by NIH and others. Workers at this centre laid the firm basis of pathology, showed conclusively that there were probably three types of poliovirus and produced the first effective vaccine. At the same time, the Yale unit under Paul and Trask had studied the epidemiology extensively; it was founded in 1932 and was later funded by the foundation. All this work led to a renewed interest in immunity and a possible vaccine. For fifteen years after the Kolmer and Park-Brodie fiascos, thoughts of a vaccine had been muted, but by 1950 sufficient knowledge had been gathered to bring an effective vaccine into the realms of possibility.

Up to this time, the funds of the foundation for scientific work had been given for a judicious blend of polio and related research. There can be no doubt, however, that the foundation regarded it all as "applied" research and that the recipients welcomed the chance to help fight poliomyelitis. They had faith in the foundation and the foundation trusted them⁸.

With the confirmation of three types of virus, the foundation contracted its first applied work. The typing programme cost \$1,400,000 and 30,000 monkeys⁹ and was wholly successful: the scientists recognized the necessity for it and four groups agreed to do it. When faced with the necessity for routine, directed, and collaborative work, the research scientists responded.

In about 1953 there were at least six people or groups who had produced vaccines. Fortunately Salk was prepared and willing to proceed. He already had experience in producing a formalin-inactivated influenza vaccine, he had the large laboratory necessary and he and his staff had experience in titrating virus and antibody. Yet the research so carefully fostered by Rivers and his committee and so successfully carried out by so many scientists could only be translated into an effective vaccine after a chance technical advance. The only source for poliovirus had been from brains and spinal cords of susceptible mammals. The work of Rivers himself¹⁰, and many others, had shown that injection of such material could give rise to experimental allergic encephalitis (EAE) in animals, and Sabin¹¹ had shown that some human adults gave a delayed type response to extracts of spinal cord. A vaccine prepared in monkey spinal cords would have been very costly and dangerous and nobody had attempted to purify such material. Fortunately, an unexpected technical advance made a killed vaccine possible. In 1949, Enders, Weller and Robbins, funded

by a National Foundation grant for basic virology, discovered that poliovirus could replicate in human non-neural tissues⁸. A few years later a similar unexpected technical advance, also funded by the foundation, made the Sabin oral vaccine possible when Dulbecco¹² invented the plaque overlay technique and enabled Sabin to clone his virus stocks. In this case, the goal was clear but the means to it were not known.

Who Represented the Consumer?

It is not easy to see how a more firmly directed programme (consumer-oriented) could have been more successful. One can, however, see how the consumer-directed bodies planned ahead and later reacted under stress. Once it had a vaccine, the National Foundation was only with difficulty persuaded to test it scientifically⁹. The trial, conducted by T. Francis (a former foundation grantee and a mentor of Salk), was a brilliant success and a classic study. The foundation, however, felt its duty to the public overwhelming, and, unmindful of possible hazards, committed itself to mass use of the vaccine in 1955. The US government, the USPHS and the standards section of NIH were all swept along. The difficulties of manufacturing the vaccine on a large scale had not been foreseen by Salk, the foundation, the manufacturing companies or the government. When difficulties arose, Salk and the companies did not appreciate them. The government department had not the means, experience or knowledge to test the vaccines for safety or effectiveness. The presence of live virulent virus in the Cutter vaccines led to 260 cases associated with vaccine, including ten deaths⁷. In some ways it was a fortunate accident: it was large enough to be recognizable as such and to be investigated. The situation, although regrettable, was certainly less severe than it might have been if the vaccine had not been used.

As a consequence, a new Division of Biologic Standards was established at NIH in a new building, safety testing was investigated and improved, the Poliomyelitis Surveillance Unit was established at CDC and international standards approved. But I believe the accident did more—it alerted scientists to the dangers and may have helped to create a climate of opinion which led to the recognition of the dangers of thalidomide. If the vaccines had been contaminated with a much smaller amount of active virus, cases might not have been noticed and the eventual toll might have been far greater.

Each time the government should have foreseen problems or become involved, it was found wanting. In the cases of the Kolmer and Park-Brodie vaccines, the Cutter incident, the licensing of the Koprowski and Cox vaccines and the use of the oral Sabin vaccine, the government was silent or called in the scientists. In the cases where large numbers of children were involved—the nasal sprays, the field trial of the Salk vaccine and the gamma-globulin trial—the government was silent. It has been suggested that development and safety testing should be carried out by the same agency. Can one agency fulfil both functions? The development problems which must be minimized may be the ones which must be perceived for the sake of safety; the researcher has to see the wood but the safety testers must be constantly falling over the trees. In the United States the separation of role was less clear in practice than on paper, for the scientists so active in polio research were also called to advise the government on safety.

Industry might also be considered as consumer-directed: but with the exception of Lederle, the pharmaceutical houses contributed little to poliomyelitis research. A few undertook to produce the Salk vaccine: all are believed to have experienced difficulty in producing a safe vaccine, some did not produce a safe vaccine and Cutter Laboratories was sued. At Lederle, Koprowski produced an oral vaccine and conducted the first trials on humans. The vaccine was used on a limited scale but was withdrawn after Dick had claimed that he had detected a reversion to neurovirulence. A Lederle-Cox oral vaccine was later used with some vaccine-associated cases in West Berlin

in 1960 (ref. 13). Sabin's oral vaccine has since been used extensively all over the world in spite of alleged vaccine-associated cases. Sabin vigorously refuted the methods and findings of those who had suggested that his strains reverted to virulence: if he is correct, the arguments would also clear Koprowski's vaccine as well. Lederle, the one commercial company to do significant research in poliomyelitis, was unlucky: the other commercial companies who produced the early Salk vaccine also made little profit.

Polio and Cancer

How much of the success of the polio story was due to the consumer-directed role of the National Foundation and how much to the vision of Rivers the scientist and O'Connor the organizer? John R. Paul gives a sympathetic picture of the National Foundation but says "the NFIP was extraordinarily lucky to have entered the arena at just the right time and to have enlisted from the start the talents of just the right man—Tom Rivers"⁸. Rivers was more than a link man between the foundation and the \$69,000,000 which it spent on research, and the scientists who received it; he was also the father of American virology. But other scientists—Paul, Enders and Bodian in particular—stand out not only for their scientific contributions but also as advisers and arbiters.

Would a centre of excellence in the form of a central National Polio Institute, either USPHS or the foundation, have supplied the answers earlier or might it have exerted a baleful influence similar to that of the Rockefeller Institute? Would the USPHS have been a better source of funds than the foundation? Would contracts earlier in the programme have been more effective? How did the propaganda that brought in the money affect the responses of the scientists to work on polio rather than other viruses or diseases? Would a similar emotional appeal to the public affect the scientists' attitude to applied research now or was polio a disease with a very special appeal? With the doubling of funds directed towards a cure for cancer, these are important questions. For, by comparison with polio, cancer is still at the pre-1909 stage.

Whatever the answers to these questions, scientists worked willingly on the consumer-directed research for prevention of poliomyelitis and much of the impetus came from the scientists themselves. Maxcy had come forward with the idea of a team of workers at Johns Hopkins; he also proposed group cooperation for typing. The impetus for the germinal round table conferences came from the scientists and from Dr Weaver, a scientist who became director of research at the NFIP. These conferences were very successful and the tradition has been carried on by the National Cancer Institute. In spite of the overall direction from the foundation, it was individual scientists who unexpectedly provided the key ideas—Dulbecco with the isolation of single viruses, Enders, Weller and Robbins with tissue culture, Koprowski and Sabin with their attenuated viruses.

Yet, curiously, three of the fundamental problems listed by the scientific research committee were never satisfactorily solved—(1) pathology of poliomyelitis in human beings, (4) transmission of virus along nerves, and (10) relation of constitution to susceptibility. The technical problem of prevention of poliomyelitis was solved in a way which bypassed these fundamental problems. Could it be that cancer will prove susceptible to technical solution without a scientific resolution?

¹ *Nature*, **237**, 63 (1972).

² International Committee for the Study of Infantile Paralysis, *Poliomyelitis* (Williams and Wilkins, Baltimore, 1932).

³ Landsteiner, K., and Popper, E., *Z. Immunitätsf. Orig.*, **2**, 377 (1909).

⁴ Wickman, I., *Acute Poliomyelitis* (English trans., Journal of Nervous and Mental Disease Publishing Co., New York, 1913). Available from Johnson Reprint Corporation.

⁵ Burnet, F. M., and Macnamara, J., *Brit. J. Exp. Path.*, **12**, 57 (1931).

⁶ Bennison, S., *Tom Rivers* (MIT Press, 1967).

⁷ Nathanson, N., and Langmuir, A. D., *Amer. J. Hyg.*, **78**, 16 (1963).

⁸ Paul, J. R., *A History of Poliomyelitis* (Yale University Press, New Haven, 1971).

⁹ Williams, G., *Virus Hunters* (Hutchinson, London, 1960).

¹⁰ Rivers, T. M., and Schwenker, F. F., *J. Exp. Med.*, **61**, 689 (1935).

¹¹ Sabin, A. B., Park, W. H., and Jungeblut, C. W., *Arch. Int. Med.*, **51**, 878 (1933).

¹² Dulbecco, R., and Vogt, M., *J. Exp. Med.*, **99**, 167 (1954).

¹³ Wilson, G. S., *Hazards of Vaccination* (Athlone Press, 1967).

Empiricism and Phenomenology

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Mr Sadler presents his reactions to an article in *Nature* by Dr R. A. Crowson on science and phenomenology.

I SUGGEST that the article by Crowson¹ expressing his strong sympathy for phenomenology does not provide a vindication for the conclusion that phenomenology provides "satisfactory basic orientations for psychologists, historians, moral philosophers, politicians" or natural historians. Much of the weakness of Crowson's article lies in the introduction of vague concepts in support of arguments which require considerable clarity and precision if the problems are to be formulated and tackled.

What, for example, could count as "satisfactory basic orientations"? His extreme emphasis on heuristic potential needs some justification. Similarly, the notion of "the most

essential reality" is far from transparently obvious. As a starting point, I would claim that the purpose of pursuits like science and philosophy is to increase our understanding of the world and to help clear up puzzles. I hope that this much can be accepted as quite basic and not subject to exceptions.

With someone who prefers an incoherent picture of nature, I have no idea how to proceed—just as in meta-ethics, one is powerless to proceed with someone who regards a universe without sentience as possessing greater intrinsic value than one with sentience.

Beliefs of Natural Scientists

It may well be that Crowson is reporting correctly when he writes that leading phenomenologists regard natural scientists as committed to the belief that the most essential reality can and should be expressed in abstract mathematical formulae. If this is what leading phenomenologists believe, then they should conduct their sociological surveys more carefully.

To start with, it is not true that there is one precisely formulated philosophy of science held by all natural scientists. The most that can be said is that many philosophically inclined natural scientists subscribe to some form of empiricism. The criterion of verifiability for meaningfulness is popular, and one thing a logical positivist could not say is that he believes that the most essential reality can and should be expressed in abstract mathematical formulae.

The historical causal genesis of this sort of expression may be due to a line of thinking suggested by Eddington, according to which we cannot, given a realist interpretation of modern physics, suppose that tables and chairs are "really" hard solids possessing smooth surfaces, because tables and chairs are composed of molecules, which are composed of atoms, which in turn have a fine structure and, if we continue our picture thinking and accept the Copenhagen interpretation of quantum mechanics, we are left regarding variables in our state equations as the square root of a probability density function. This line of reasoning relies for its appeal on the gross misuse of words. It assumes that because the predicates "hard", "solid" and "smooth" cannot meaningfully be predicated at the micro-level when used with their ordinary meanings, they cannot be correctly applied to macroscopic objects like tables and chairs. It is surely reasonable to reject this assumption².

I do not wish to suggest that the relation between mathematics and physics is transparently obvious. Husserl, who had received some mathematical training, went to some pains to refute J. S. Mill's view that mathematical knowledge is based on empirical generalization. Some modern empiricists regard mathematical knowledge as analytic *a priori*. Nevertheless, I think Quine³ is correct to emphasize that the analytic-synthetic distinction is not completely sharp. Our concepts have theories built into them from the start. Our fundamental physical laws are like the principles of mathematics and logic to the extent that they cannot be overthrown by isolated experiments. It is always possible to retain the laws and explain our results in a more or less *ad hoc* way. Furthermore, this is surely the reasonable approach to take for as long as no acceptable alternative theory is available.

The role of the conservation of energy in modern physics is a case in point. We cannot today describe any experiments which would overthrow it, although the law is not analytic and might be abandoned if there were good theoretical reasons for doing so and positive supporting experiments⁴.

It would seem central to both Sartre and Husserl to get "back to the things". It may well be the case that our brain structure is such that it leads infants to hypothesize one of a limited number of types of grammar⁵. This offers, however, no support for mapping the subject-predicate structure of the natural Indo-European languages onto world structure.

In any case, in Chinese, so I am informed, the very notion of substance does not occur, because the language is not of subject-predicate form. As the grammar of our language reflects a conceptual scheme, it is clearly related to the issues of theory neutrality. The natural European languages use nouns, adjectives, and so on, whereas an artificial language uses such things as quantifiers, variables, and predicates. Many of the puzzles which arise in Meinong and Husserl can be dealt with by adopting an adequate "theory of descriptions"^{6,7}, that is, very briefly, "The golden mountain does not exist" ceases to be puzzling when presented symbolically as: (x)—(x is golden and x is mountainous), or more loosely in colloquial usage: "There is nothing which is both golden and mountainous".

Even if, somehow, the study of neurophysiology and psycholinguistics should eventually lead us to the conclusion that our innate brain structure is such as usually to cause us to formulate our ordinary conceptual schemes of substance and change, this only leads to the conclusion that these conceptual schema have, until now at any rate, provided good survival value, and not that they are metaphysically basic.

It often happens that an incorrect theory is more practically

useful than a correct one. Commonsense language may merely be a convenient bridge to the development of a more adequate scientific language using quantification theory and the concepts of four-dimensional space-time objects rather than three-dimensional objects evolving in time.

On Contingency

Crowson wishes to focus attention on the notion of contingency. Colloquially, one describes a state of affairs as contingent if it may or may not happen. More precisely, a logically contingent statement is contingent with respect to the laws of logic, for example, the truth value of " $p \vee q$ " is contingent on the truth values of " p " and " q ". A physically contingent statement is contingent with respect to the (assumed known) laws of nature. It seems odd for Crowson to write: "Natural philosophers tend to consider everything which is not a strictly conducted experiment in a laboratory as contingent". The function of strictly conducted laboratory experiments is to create information—and clearly this they cannot do unless they are contingent. No information is gained from the result of an experiment if the result could not have been otherwise. It is easy to illustrate this point further by referring to an article in *Nature*⁸, which was accompanied by the publishing of the referee's report. The first sentence of the article asserts that experiments have shown that the velocity of light is independent of the velocity of the source to a high degree of accuracy. The referee comments that from a relativistic point of view, the possibility of dependence of the velocity of light on the velocity of the source does not arise because the independence is a tautology. The referee goes on to deplore that after half a century of relativity, physicists should still think in terms of (quasi) Newtonian concepts.

In metaphysics, contingency is the opposite of determinism, that is, it is held that some events are uncaused. It would seem that it is this metaphysical sense of contingency which is accepted by phenomenologists. To regard the principle of causality as an empirical generalization in the manner of J. S. Mill can be shown to amount to merely giving an implicit definition of what it is to be a determining factor². It is a historical fact that the enterprise of natural science has proceeded by accepting determinism as at least a methodological rule for enquiry. As an overall view, many natural scientists would seem to take a soft determinist line. Even for Sartre, the attempt to rationalize the world is rejected. Exactly this point had already been covered in traditional British empiricism which maintains that "brute factuality" cannot be explained away as necessity in disguise. The general objective of theoretical science is to achieve deterministic explanations governed by laws, that is, given an initial state of the system, the explanatory theory logically established a unique state existing at any other time. This general formulation has the advantage of not prescribing a particular definition for the state descriptions, that is, statistical or quasi-statistical state variables are acceptable. It is logically possible that men could have sought to understand their environment by adopting a different maxim for enquiry—the principle is not a synthetic *a priori* truth. Thus, the acceptance of the principle of causality as a maxim of enquiry is an analytic consequence of what is commonly meant by natural science.

Natural Science and Natural History

I further maintain that there is no very deep distinction between natural science and natural history. The drawing of a deep difference dates back at least to the time of Aristotle. He regarded natural science as "more philosophic and of graver import" than history, as the latter is concerned with the special and singular. This *prima facie* difference, however, needs examination. It can, I think, be agreed that natural history is concerned with particular facts about our terrestrial environment; palaeontology, for example, is

concerned with the relating of a historical narrative. Also, even though geology makes use of very general physical laws for explanation of particular facts, this does not detract from its status as history, for its chief concern is with the particular facts themselves and not with particular facts regarded as tests of physical laws. Thus, a geologist doing a radiometric survey of some minerals is not concerned with the physical basis of β decay. As regards to the natural sciences, however, it is worthwhile to emphasize that their general statements cannot be asserted as empirically warranted except by establishing and using singular statements. Kepler formulated his laws to apply only to the solar system. The extension to any system of bodies gravitating under an inverse square law is a generalization. Similarly, we could suppose it to be a biological law that a leopard cannot change its spots. When this is expressed in the form: $(x) (x \text{ is a terrestrial leopard} \supset x \text{ cannot change its spots})$, it is true everywhere. The detail of biological evolution on our planet is a study in terrestrial history. Nevertheless, it would seem a legitimate function of biologists to concern themselves with propositions about evolution, which are more general in the sense that they are applicable anywhere and at any time in the universe, for example, the statement that carbon is essential to any life form may be true, or it may be false. It would be interesting to know which⁹⁻¹¹.

Other Points

The remaining points of Crowson's article I shall deal with very briefly. Empirical ethical theories have been influential at least since the time of Bentham. The manner in which shape words, lens-shaped, grooved, and so on, which are deliberately vague are accounted for within the framework of a fairly orthodox empiricism, is discussed by Hospers¹². Bergson's theory of time has some romantic appeal, but little else to recommend it. I do not think that Husserl's theory provides any trouble for an identity theory of mind (central state materialism). When one says: "I am thinking about the Melbourne Cup", only a rough similarity of abstract structure of brain states and the physical event, which is the horse race, is required. There are various discussions of the intentionality of our thoughts in ref. 4.

One point of methodology in which Crowson acquiesces seems to me particularly undesirable. He would wish to claim that while phenomenology is an appropriate belief for natural historians, it is not (at present at least) appropriate for natural scientists. (In fact, at least one quite eminent mathematical physicist was, at one time, influenced strongly by Husserl's phenomenology¹³.) To take this line seems to me to give up too easily. I would judge the attempt to see the world as a complete whole to be worthwhile for its own sake.

Dr Crowson replies:

SADLER's comments on my article on science and phenomenology provide almost a textbook example of the mutual misunderstandings which are liable to affect communications between practising scientists on the one hand and formal philosophers on the other. Sadler writes in the manner of a professional philosopher, judging ideas by current academic standards of logical coherence. In this sphere, he is no doubt much better qualified to speak than I, and it would be very rash of me to try to criticize his logic. My article was, however, written—though perhaps this was not made sufficiently clear at the time—from the point of view of a natural historian, after seeking in the writings of various schools of philosophy for a fundamental intellectual attitude which could be reconciled with his own intellectual practices and experience. In the domain of natural history (which is more fully defined and discussed in ref. 1), I have considerable experience and may well be better qualified to draw general conclusions than is Mr Sadler.

One point of agreement between us is that, in his phenomenology, Husserl tried to reassert the fundamentality of perceived things as opposed to mental schemata; this attitude would tend to link Husserl with natural history rather than natural philosophy. Sadler maintains, however, that "there is no very deep distinction between natural science and natural history"; Aristotle is cited for the opinion that natural science is "more philosophical and of graver import" than history. For the Stagyrte, however, history would have meant human history only, and natural science would have included natural history, so that the quoted opinion is strictly irrelevant to this discussion. Sadler, incidentally, never makes it quite clear whether his "natural science" is equivalent to my natural philosophy.

The most difficult issues involved in the differences between us are concerned with contingency. The concept of the contingent seems to be present in one form or another, more often implicitly than explicitly, in most previous philosophical systems, although I have yet to read a work which provides a satisfying definition and treatment of it. Sadler's colloquial definition, that an event is contingent "if it may or may not happen", is probably as useful as any of the more elaborate ones I have seen. According to anti-historicist philosophers like Karl Popper, the whole of (human) history is a catalogue of contingencies, so defined. It would be a logical extension of the Popperian attitude to apply it also to the entire domain of organic evolution and its products, comprising the subject matter of virology, bacteriology, botany and zoology. In most academically respectable philosophical systems, to refer any phenomena to the realm of the contingent is to banish them to a sort of limbo, where no philosophical significance is to be found.

For positivists, Cartesians and similar schools, the whole domain of natural history is liable to be equated with that of contingency, and thus to be excluded from serious philosophical consideration. Sadler deplores my suggestion that no formal philosophical system yet proposed, which would satisfy his canons of logical coherence, could provide an adequate intellectual basis for all types of human activity, scientific, artistic, moral and political. Regrettable or not, this seems to me to be a plain statement of fact, exemplified by the failure of current scientific philosophies to attribute any philosophical significance to natural history. It is entirely characteristic that the name of Charles Darwin, and the topic of organic evolution, make no appearance in the index to *The Logic of Scientific Discovery*. I agree with Sadler in wishing that we could all share a universal philosophy, but suspect that, if such a philosophy ever comes to exist, it will violate some of his canons of logical coherence.

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Trace Elements in the Atmospheric Environment

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The origins of atmospheric trace elements measured in the vicinity of Lake Windermere are indicated by relationships derived between the levels in air, rain and dry deposition.

TRACE elements in airborne dust arise from the Earth's surface and also descend from sources beyond the atmosphere¹. The terrestrial aerosols are raised from the surface of land and ocean by winds, by the eruption of volcanoes and by industrial activities.

Larger particles ($>10\ \mu\text{m}$) will promptly return to the surface by sedimentation, but smaller particles may be raised by updraughts and turbulence to higher altitudes, so that dispersal is more widespread; particles reaching the stratosphere will eventually be distributed on a worldwide scale: those that remain in the troposphere will be transported in the zonal circulation before returning to the Earth's surface². Aerosols are transferred to the Earth's surface by wet deposition through precipitation and by dry deposition through sedimentation, impaction and diffusion³.

Trace elements in the atmosphere, in the ground and in water can be considered in three roles: (a) as nutrients, (b) as potentially toxic pollutants and (c) as tracers of transfer mechanisms. It is necessary to determine the background levels of trace elements and the natural and unnatural variations about these levels, to observe the passage of the trace elements through the environment. It follows that knowledge is required of the transfer mechanisms of trace elements between air, rain, water, vegetation and so on, and of the corresponding deposition inventories. Other analyses of the atmospheric environment have often been restricted to trace elements in air, to urban areas or to short sampling periods⁴⁻¹⁴. Less information is available on the composition of rainwater¹⁵⁻²⁰.

The present exploratory programme of environmental analysis was established to determine the levels and immediate fate of atmospheric trace elements at a single location. The programme was sponsored by the Natural Environment Research Council, who selected a relatively unpolluted site near Lake Windermere (Westmorland) for the measurements in the field. Since April 1970, there has been continuous sampling, using weekly or monthly periods, not only of airborne dust near ground level but also of rainwater, and from

November 1970 samples of the dry deposition have been collected as well. Samples have been analysed for about 30 trace elements.

The site chosen for sampling is at Wraymires (grid reference SD362974), 84 m above sea level and with an annual average rainfall of 180 cm. The nearest heavy industry is 30 km towards the south-west, at Barrow-in-Furness. The methods of sampling were made simple in order to obtain continuous and trouble-free operation in a remote area. Samples of airborne dust were collected by drawing air through filter papers held in polypropylene ducts. Rain was collected in a

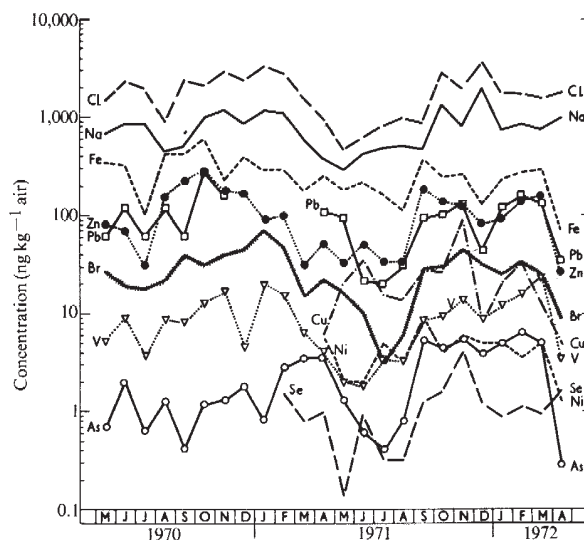


Fig. 1 Elemental concentration in air near ground level at Wraymires (1970-72).

polythene funnel and bottle, which would contain the total deposition—that is, the wet deposition plus the dry deposit on the funnel that was washed in by subsequent rain. Dry deposition was collected on a horizontal sheet of filter paper sheltered beneath a plastic cover to shield the surface from rain. Most of the trace element analyses were made by neutron activation of the sample followed by gamma ray spectrometry²¹⁻²⁴, although for lead, nickel and cadmium, for example, X-ray fluorescence has proved convenient and economical²⁵.

Composition of Deposits

Some 30 elements have been determined quantitatively in aerosol samples from Wraymires, either as weekly or monthly concentrations. In addition, nine other elements have been qualitatively identified. The highest concentrations have been $\sim 1 \mu\text{g kg}^{-1}$ of air, in the case of Cl, Na and Ca. Next in abundance are Al, Fe, Pb and Zn. The total mass of particulates was about $20 \mu\text{g kg}^{-1}$ of air. Over the limited period of measurement there was a general increase in the concentrations in air during the winter compared with summer, as demonstrated in Fig. 1, for a number of the elements measured. This we attribute to the seasonal reduction in the vertical diffusion in the atmosphere; it is associated with the increased frequency of temperature inversions during the winter²⁶. The rain concentration results combine the measurements of the soluble and insoluble contents. The soluble component is probably more available biologically and in future studies should be considered separately.

Certain derived parameters, "washout factor" W and "dry deposition velocity" V_g , are summarized in Table 1 together with the total deposition T and dry deposition D , all as mean monthly values during the year 1971. The magnitudes of total deposition generally follow those of the air concentrations: the proportion of dry deposition D/T is shown in Table 1. In the case of certain trace elements, Al, Sc, V and Fe, the dry deposition amounts on average to 15% or more of the total, although occasionally over shorter periods the dry deposition can account for more than half the total.

The washout factor W has been defined by Chamberlain³ as

$$W = \frac{\text{concentration in rain } (\mu\text{g kg}^{-1})}{\text{concentration in air } (\mu\text{g kg}^{-1})}$$

and the manner in which this parameter averaged over 1971 varies according to element is shown in Fig. 2. Despite the variation over five orders of magnitude in air and rain concentrations the washout factors lie between 500 and 2,000 except for Na, Cl and Se. Within this range it is nevertheless possible to differentiate broadly between the trace elements, in that those having higher values of W are more easily washed out and therefore have higher concentrations in the atmosphere at the rain forming altitudes ($\sim 3 \text{ km}$), compared with ground level, than do the trace elements having lower values of W . It follows that high W is associated with a greater dispersion in altitude and therefore with a distant source whereas low W is associated with a more local source.

The dry deposition velocity V_g has been defined³ as

$$V_g \text{ (cm s}^{-1}\text{)} = \frac{\text{rate of dry deposition } (\mu\text{g cm}^{-2} \text{ s}^{-1})}{\text{concentration in air } (\mu\text{g cm}^{-3})}$$

The dry deposition velocities averaged over 1971 are displayed in a similar way in Fig. 3; most are seen to lie between 0.1 and 0.7 cm s^{-1} . The relationship between the mechanistic theory of dry deposition and our observations is not clear, especially when considering the effects of particle size, surface

Table 1 Annual Summary of Wraymires Results (January–December 1971)

	Concentration in rain ($\mu\text{g l}^{-1}$)	Concentration in air (ng kg^{-1})	Washout factor W	Parameter (annual mean)		D/T ratio	Dry deposition velocity V_g (cm s^{-1})
				Total deposition/month T ($\mu\text{g cm}^{-2}$)	Dry deposition/month D ($\mu\text{g cm}^{-2}$)		
Na	2,300	800	2,900	27.5	1.35	0.05	0.53
Al	160	260	620	1.90	0.36	0.19	0.44
Cl	4,100	1,750	2,300	48.5	2.50	0.05	0.44
Ca	<1,100	520	<2,100	<13	0.95	0.06	0.57
Sc	0.042	0.059	710	0.0005	0.00019	0.38	1.01
V	4.1	8.0	510	0.049	0.0075	0.15	0.29
Cr	2.9	2.4	1,200	0.035	0.0022	0.06	0.29
Mn	8.1	10.6	760	0.096	0.008	0.08	0.24
Fe	200	230	890	2.35	0.41	0.17	0.57
Co	0.25	0.32	780	0.003	0.0003	0.10	0.29
Ni *	<6	5.5	<1,100	<0.07	<0.02	—	<1.1
Cu *	23	26	880	0.27	0.006	0.03	0.07
Zn	85	80	1,050	1.00	0.051	0.05	0.20
As	1.6	2.5	640	0.019	0.0019	0.10	0.24
Se *	0.34	0.90	380	0.004	0.00026	0.07	0.09
Br	17.0	27.1	620	0.20	0.017	0.09	0.20
Rb *	0.67	1.04	640	0.008	<0.00012	<0.15	<0.04
Cd *	<17.7	<3	—	<0.21	<0.02	<0.1	—
In *	<0.59	0.3	<2,000	<0.007	<0.0007	—	<0.73
Sb	1.8	1.6	1,150	0.021	0.00027	0.01	0.05
I	<2.5	<2.2	—	<0.03	<0.0004	—	—
Cs *	0.17	0.16	1,050	0.002	0.00012	0.06	0.23
La *	<0.3	<0.5	—	<0.004	<0.0005	<0.3	—
Ce *	0.42	0.30	1,400	0.005	<0.0005	<0.1	<0.52
W *	0.35	<0.86	—	<0.004	<0.0009	—	—
Au	0.01	<0.01	—	0.00011	<0.00001	—	—
Hg	<0.2	<0.17	—	<0.002	<0.0002	<0.1	—
Pb *	39	87	450	0.46	<0.05	<0.1	<0.18
Th *	0.12	0.13	920	0.001	0.0002	0.10	0.48

* Incomplete data.

Annual rainfall 142.7 cm.

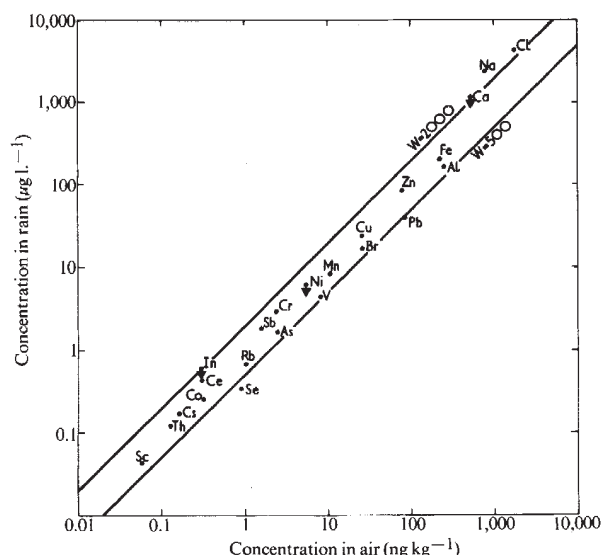


Fig. 2 Elemental concentrations in air and rain at Wraymires (1971).

roughness, wind velocity and other natural parameters. An important relationship in the present context is that between V_g and particle diameter d , and a semi-quantitative impression can be obtained from theory and data published by Chamberlain²⁷. Broadly, the curve of V_g passes through a flat minimum in the region $10^{-1} \mu\text{m} < d < 1 \mu\text{m}$. Below this region V_g increases as gaseous diffusion becomes important: above, V_g becomes the terminal velocity due to gravitation at $d > 10 \mu\text{m}$. The only quantitative scale, appropriate to the present experimental arrangement, that can be applied to V_g is derived from the measurements of radioactive fallout^{28,29}. If $V_g = 0.2 \text{ cm s}^{-1}$ for $d \sim 0.5 \mu\text{m}$ then the range of values of d for the trace elements in Fig. 3 might lie between $0.1 \mu\text{m}$ and $10 \mu\text{m}$; V_g increases with d . This is necessarily a simple interpretation and may be appropriate only to this method of collection. Thus it is unlikely that a natural aerosol can be represented by a single value of d , which must be characteristic of the property of the aerosol involved in the measurement of d .

Natural Origins of Trace Elements

It is now possible to review the possible origins, natural or artificial, of the trace elements measured at Wraymires by making use of the experimental observations, the derived

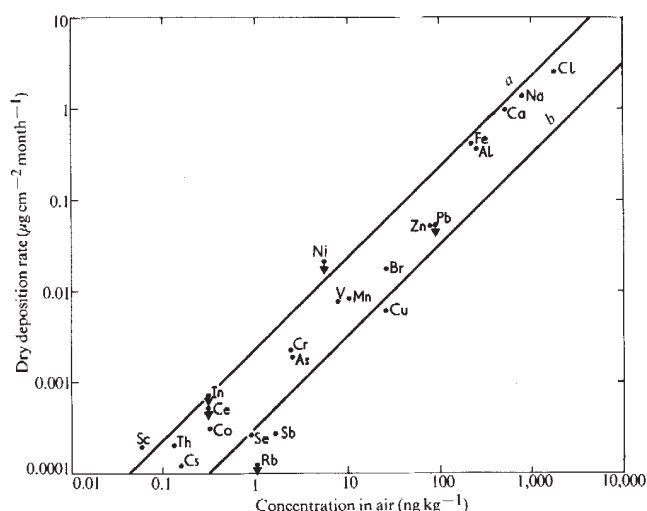


Fig. 3 Dry deposition and elemental concentrations in air at Wraymires (1971). a, $V_g = 0.7 \text{ cm s}^{-1}$; b, $V_g = 0.1 \text{ cm s}^{-1}$.

parameters and other more general information. The summary values for V_g and W averaged over the year 1971 are combined in Fig. 4.

The ratio Cl/Na in air (2.2) is similar to but somewhat higher than the ratio in seawater (1.8): this similarity indicates a predominantly maritime origin for these two elements as does the correlation with wind direction (Briggs, private communication). Large values of washout factor W for Na and Cl suggest favourable conditions for washout; that is significant concentrations at the rainforming altitudes ($\sim 3 \text{ km}$) compared with ground level. The large particle sizes implied by the large values of the dry deposition velocities V_g are consistent with the hygroscopic nature of sodium chloride, thus further increasing the susceptibility to washout. The excess of Cl over the seawater proportion is probably industrial in origin as W is significantly lower than for Na. An increase in the ratio Cl/Na to > 2 in the winter months had been noted previously in rainwater at Windermere by Gorham³⁰, who suggested that combustion of coal was responsible for the increase in Cl. All other trace elements except Br measured at Wraymires are present in seawater at such low concentrations relative to Na that a maritime origin is unlikely.

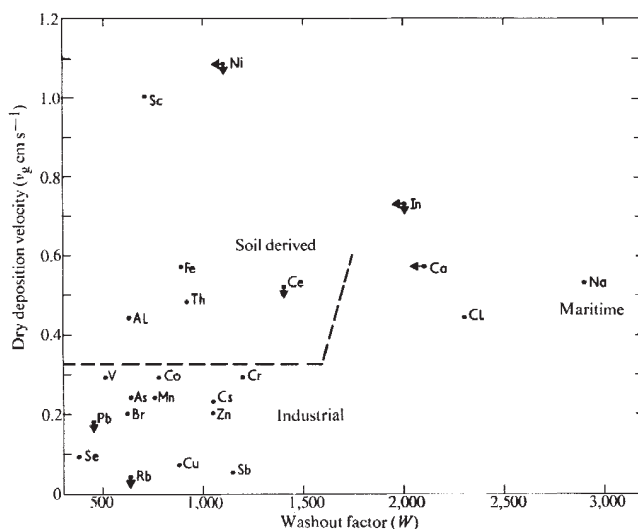


Fig. 4 Dry deposition velocity and washout factors at Wraymires (1971).

The other natural source of airborne trace elements is the soil, from which aerosols are raised by passing winds. The concentrations in air and rain may be compared with those measured in a sample of local soil (Grizedale series) and in soil generally, as listed by Bowen³¹. For convenience all concentrations are made relative to Sc, considered to be largely soil-derived, an assumption confirmed by high V_g and low W . Al, Mn (?), Fe, Rb, Ce and Th have approximately the same concentrations, relative to Sc, in air and soil; these elements, except Mn and Rb, lie in the sector of Fig. 4 that corresponds to high V_g , hence large particle size, and (except Ce) to low W , hence confinement to low altitudes. All other elements measured have concentrations in air relative to Sc greater or much greater than in soil, in particular Cl, Cu and Pb. A recent study by Rahn and Winchester¹² in Canada and Michigan suggested that most elements associated with larger aerosol particles, such as Al and Fe, had soil dust as their main source.

Other Sources of Particles

Those elements that are neither derived from the sea nor soil presumably have artificial origins. Generally, industrial

processes involving combustion will yield small particles ($<1\ \mu\text{m}$) formed by condensation, whereas natural particles formed by wind erosion and by grinding will be larger as noted above. Most of the trace elements that might be associated with artificial or industrial production lie conveniently in the sector of Fig. 4 below that of the soil derived elements. The trace elements of artificial origin have low V_g , corresponding probably to diameters $<1\ \mu\text{m}$, and low to moderate W , implying sources ranging from local to more distant. Thus a likely origin for V is in fuel oil, and it is probable that the increase during winter⁹ in the combustion

the first is present at Wraymires in notable concentrations in the air samples collected. The incomplete data for Pb are consistent with a low V_g and low W suggesting small particles formed in combustion locally. Lead is frequently attributed to motor vehicle exhausts, perhaps in association with Br. The ratio of concentrations in air Pb/Br ~ 3.2 (Table 1) compares with the value of 2.6 in ethyl fluid reported by Lininger *et al.*³⁴.

Of the trace elements that do not fall readily into the "maritime", "soil derived" and "industrial" categories of Fig. 4, the values of V_g and W for Ni and In are too uncertain for reasonable deduction. An anomalous position in Fig. 4

Table 2 Comparison of Air Concentrations at Seven Sites in the UK, January–March, 1972

Element	Chilton, Berks	*Leiston, Suffolk	Lerwick, Shetland Is.	Plynlimon, Montgomery	†Styrrup, Notts	Trebanos, Glamorgan	Wraymires, Lancs
Na	650	1,620	3,430	400	920	840	790
Al	370	430	89	143	580	300	150
Cl	2,040	3,080	5840	920	4,180	2,130	1,750
Ca	550	<50	<50	<50	<50	<230	<200
Sc	0.10	0.089	0.019	0.032	0.15	0.17	0.05
V	22	19	3.5	5.4	26	20	17
Cr	3.6	14	1.4	1.0	12	11.1	2.7
Mn	21	38	4.3	8.2	49	20	15
Fe	380	549	102	160	785	502	271
Co	0.41	0.59	0.10	0.19	0.65	4.8	0.21
Ni	6.4	5.2	1.2	<5	9	54	<4.5
Cu	22	27	<1	18	55	40	22
Zn	194	327	64	117	415	302	132
As	6.5	8.5	2.5	2.0	19.3	7.5	5.4
Se	1.5	1.8	0.55	0.40	2.5	1.4	0.95
Br	48	34	18	11	102	46	28
Rb	<0.3	<0.3	<0.3	<0.3	<0.3	<1	<0.3
Cd	<4	<5	<4	<5	<5	<18	<4
In	<0.03	<0.03	<0.03	<0.03	<0.03	<0.1	<0.03
Sb	2.9	3.7	0.66	0.46	4.5	2.4	1.9
I	<0.1	<0.1	<0.1	<0.1	<0.1	<0.4	<0.4
Cs	0.30	0.51	0.09	0.11	0.51	0.27	0.20
La	<0.3	<0.3	<0.3	<0.3	<0.3	<1	<0.3
Ce	0.40	0.39	0.11	0.16	0.54	0.31	0.25
W	<0.3	<0.3	<0.3	<0.3	<0.3	<1	<0.3
Au	<0.003	<0.003	<0.003	<0.003	<0.003	<0.01	<0.003
Hg	0.15	<0.05	<0.07	0.05	0.09	0.24	0.13
Pb	98	103	43	35	380	208	139
Th	0.06	0.04	<0.03	<0.03	0.05	0.13	0.10

Concentrations are in ng kg^{-1} air.

* Leiston—data available for February and March only.

† Styrrup—data available for January and February only.

of fuel oil for heating will enhance the seasonal variation noted previously. A fraction of Br may be maritime, on the basis of seawater concentrations relative to Na, but most is of industrial origin, either in fuel oil or as an ingredient of petrol. The ratio of concentrations in air Br/V ~ 3.5 (Table 1) is similar to that found by Dams *et al.*⁷ in Chicago. If the somewhat larger values of W for Cr, Sb, Cs and Zn are significantly different from those for the other artificial trace elements, then the former are likely to arise from the more distant sources. Iodine does not appear in Fig. 4 because the values of the derived parameters are indeterminate, but the occasional positive indications ($>1\ \text{nano g kg}^{-1}$) of air could arise from the combustion of coal and oil^{32,33}. Of the potentially toxic group of metals Pb, As, Se, Ni, Cd and Hg, only

is occupied by Ca, which is unlikely to arise from a natural source in the quantities determined, although both V_g and W (upper limit) seem too high for artificial production by a combustion process.

Extensions of the Study

The concentrations measured in air at Wraymires have been compared with results obtained by other workers overseas^{6,10,12,35}. Elements showing >10 -fold increases relative to Wraymires in concentration in air from industrial regions in Japan¹⁰ and the USA^{6,35} are Mn, Fe, Zn, As, Sb, La, Ce, W and Hg. However, with the exception of Ce, the elemental concentrations in air at Wraymires exceed those reported for

rural Canadian stations^{1,2} which suggests that the Wraymires atmosphere is influenced by distant industrial activity.

The methods of sampling and analysis, the assessments of these methods, the measurements of trace elements in air, rain and dry deposition and a correlation with wind speed and direction have been described in detail elsewhere (AERE-R7134, in preparation). Finally, the programme of sampling and analysis at Wraymires has been extended to six other stations in the UK. To show how the results from Wraymires compare with levels from other non-urban sites, the concentrations of trace elements in air are listed in Table 2 for the first quarter of 1972.

We received help in the sampling arrangement and advice from the late F. J. H. Mackereth of the Freshwater Biological Association at Windermere.

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Wheat Germ Agglutinin blocks Mammalian Fertilization

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Wheat germ agglutinin specifically binds to the zona pellucida of hamster eggs and prevents sperm penetration and fertilization.

BEFORE fertilizing mammalian eggs, spermatozoa pass through a moderately thick transparent egg coat, the zona pellucida (ZP). There is evidence that the ZP is an important site for the species-specificity of fertilization¹⁻³ and the

block to polyspermy^{4,5}. The ZP has been characterized as glycoprotein or glycopeptide in nature⁶⁻⁸, and it can be dissolved by proteolytic enzymes⁹⁻¹³, oxidizing agents⁹ and disulphide-reducing agents^{6,13,14}.

Characterization of ZP-Modifying Component

We found that hog pancreatic lipase (Sigma Chem.) dissolved the ZP of hamster eggs, but a crude wheat germ lipase preparation (Sigma Chem.) did not. Pretreatment with crude wheat germ lipase prevented dissolution of the

ZP by trypsin, pronase, papain, bromelain, ficin and also hog pancreatic lipase. The wheat germ lipase preparation increased the light-scattering properties of the outer surface of the ZP and prevented ZP penetration by spermatozoa.

Fractionation of the crude wheat germ lipase preparation yielded a "ZP-modifying", non-dialysable component that was heat-stable (30 min at 90° C). The molecular weight of this component was approximately 20,000–30,000 daltons, as shown by gel filtration chromatography using 'Sephadex' G-100, G-75 and G-50 and polyacrylamide gel electrophoresis. The size, heat-stability and the fact that the purified "ZP-modifying" component was capable of agglutinating rabbit erythrocytes suggested that it might be wheat germ agglutinin (WGA), a phytoagglutinin purified from a crude wheat germ lipase preparation¹⁵ that specifically binds to oligosaccharides containing terminal (non-reducing) N-acetyl-D-glucosamine (NAGlcA) residues¹⁶. This was subsequently

exposed to a solution of 0.01% hog pancreatic trypsin (Trypsin 1–300, Nutritional Biochem.) or 0.1 M β -mercaptoethanol in 0.9% NaCl–0.01 M Tris-HCl (pH 7.4 at 25° C) to dissolve the ZP. The remainder of the eggs were tested for their fertilizability. One drop (50 μ l.) of a suspension of cauda epididymal spermatozoa in Tyrode's solution was placed under mineral oil (Squibb Products Co.) in a watch glass and mixed with an equal volume of detoxified human serum¹⁹. After incubation for 4 h at 37° C the spermatozoa were considered to be capacitated, that is, capable of fertilizing hamster eggs. The eggs in approximately 20 μ l. of Tyrode's solution were introduced into the suspension of capacitated spermatozoa, mixed and then incubated for 2 h at 37° C. Finally, the eggs were rinsed with Tyrode's solution and examined using phase-contrast microscopy for evidence of sperm penetration through the ZP and into the egg cytoplasm.

Table 1 Effects of Wheat Germ Agglutinin on the Hamster Egg Zona Pellucida

Experiment	Treatment	WGA concentration (μ g ml. ⁻¹)							
		0	1	5	10	50	100	250	500
Light-scattering*	WGA†	—	—	—	+	+	+	+	+
	WGA→NAGlcA‡	—	—	—	—	—	—	—	—
Resistance to trypsin§	WGA†	—	—	+	+	+	+	+	+
	WGA→NAGlcA‡	—	—	—	+	+	+	+	+
Resistance to β -mercaptoethanol§	WGA†	—	—	—	—	+	+	+	+
	WGA→NAGlcA‡	—	—	—	—	—	+	+	+
Sperm penetration	WGA†	106/106	18/18	14/14	9/15	0/21	0/100	0/50	0/6
	WGA→NAGlcA‡	82/82	16/16	15/15	25/26	11/30	0/19	0/29	0/7

* The outermost region of the zona pellucida scatters light strongly (+) or does not scatter light (—) under dark-field illumination.

† Eggs treated with various concentrations of wheat germ agglutinin for 30 min at 25° C and washed three times by transfer.

‡ Eggs treated similarly but were then incubated in a solution containing 0.1 M N-acetyl-D-glucosamine for 15 min.

§ Treatment with 0.01% trypsin or 0.1 M β -mercaptoethanol solution at 25° C. +, Failure to dissolve the entire zona pellucida within 30 min; —, zona pellucida completely dissolves within 5 min.

|| Ratio of the number of eggs showing spermatozoa penetration of the zona pellucida within 2 h after *in vitro* insemination with capacitated spermatozoa to the total number of eggs used in three different experiments.

established by the following experiments: (a) molecular weight determination using gel chromatography and polyacrylamide gel electrophoresis; (b) agglutination properties (including inhibition by NAGlcA), and (c) immunological cross-reaction with WGA (purified by affinity chromatography)¹⁷ in double diffusion tests with rabbit anti-WGA serum in the presence of NAGlcA. We therefore used affinity purified WGA in further studies.

Binding of WGA to the Zona Pellucida

Unfertilized eggs were collected from adult female golden hamsters 16–17 h after injection of human chorionic gonadotropin¹⁸. Eggs were freed from cumulus cells by treatment for 15 min with Tyrode's solution containing 0.1% bovine testicular hyaluronidase (300 USPU mg⁻¹, Nutritional Biochem.). After thorough washing with Tyrode's solution, the eggs were incubated for 30 min at room temperature (about 25° C) in 0.9% NaCl–0.01 M Tris-HCl, pH 7.4, containing various amounts of purified WGA. After incubation with WGA, the eggs were rinsed three times for 5 min each in Tyrode's solution or isotonic 0.59% NaCl–0.1 M NAGlcA (WGA inhibitor), and some of the eggs were examined under dark-field illumination. Other eggs were

When hamster eggs are treated with WGA, it binds to the outer region of the ZP. WGA (10–500 μ g ml.⁻¹) causes the outermost region of the ZP to scatter light strongly under dark-field illumination (Fig. 2; this can be compared with Fig. 1, an untreated egg, for the relative position of the ZP to the egg). The light-scattering properties of the ZP disappear after washing the WGA-treated eggs with an NAGlcA solution (Fig. 3 and Table 1). Other saccharides (sucrose, D-galactose, L-fucose and N-acetyl-D-galactosamine) fail to affect or reverse the ZP light-scattering properties caused by WGA. Further evidence that WGA binds to the outermost region of the ZP is that ferritin-conjugated WGA exclusively binds to this region, but not when NAGlcA is present (G. L. N. and R. Y., unpublished observation).

The outer region of the ZP is resistant to trypsin or β -mercaptoethanol dissolution after WGA treatment (Table 1). Concentrations of WGA greater than 5 μ g ml.⁻¹ prevent trypsin dissolution of the outer region of the ZP when assayed 30 min after initiation of trypsin treatment (Fig. 4; compare with Fig. 5, an egg not treated with WGA). If the WGA concentration is 10 μ g ml.⁻¹ or more, trypsin dissolution is prevented for at least 12 h. The trypsin resistance can be reversed by subsequent NAGlcA treatment when the eggs are preincubated with a low WGA concen-

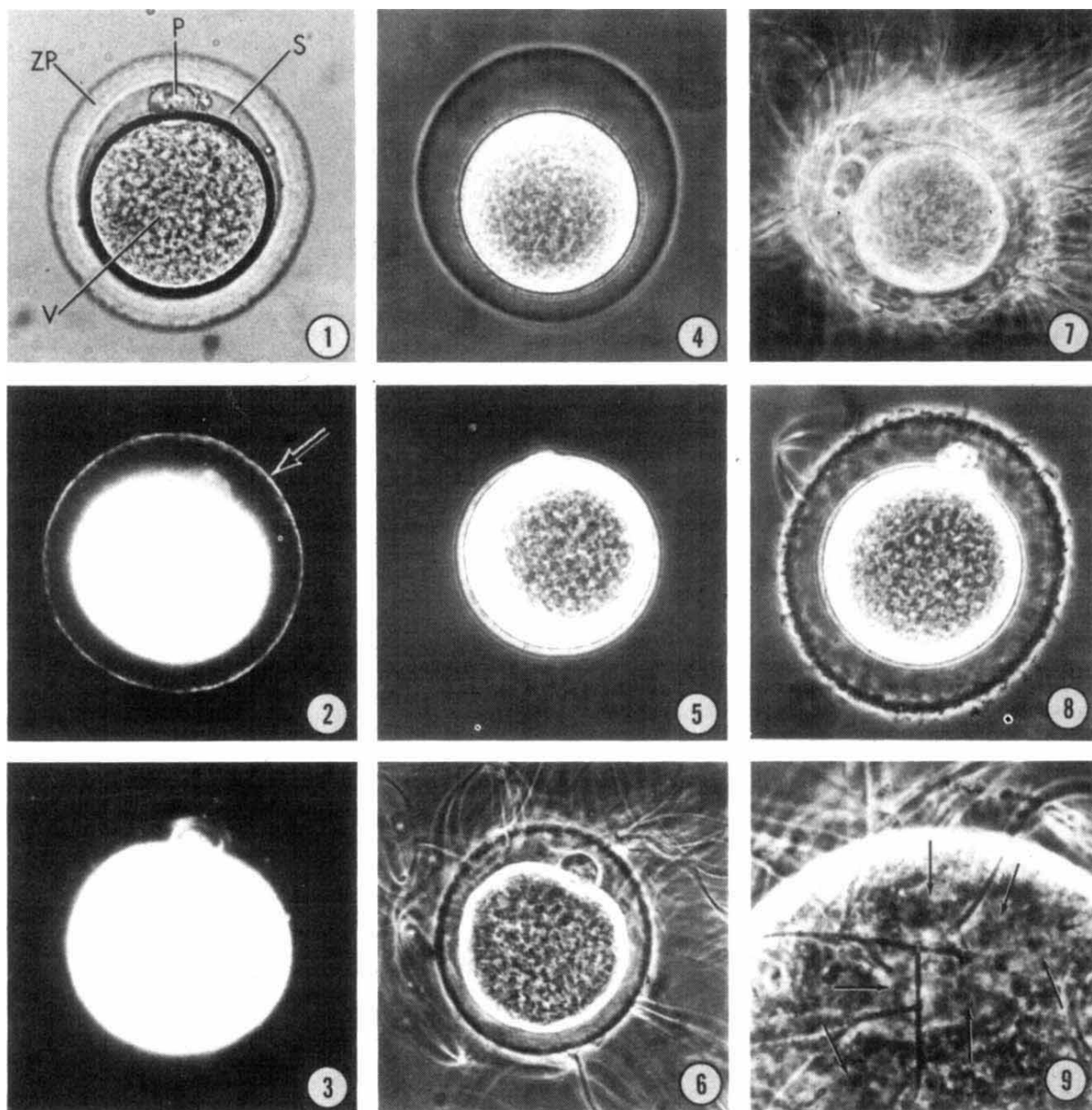


Fig. 1 Unfertilized hamster egg photographed with bright field light microscopy, showing the general structure of the egg. P, First polar body; S, perivitelline space; V, vitellus or egg proper; ZP, zona pellucida. $\times 380$.

Fig. 2 Unfertilized egg treated for 30 min with wheat germ agglutinin ($100 \mu\text{g ml}^{-1}$), showing strong light-scattering on the outer surface of the zona pellucida (arrow). Dark field, $\times 380$.

Fig. 3 Unfertilized egg exposed to 0.1 M N-acetyl-D-glucosamine for 15 min after wheat germ agglutinin pretreatment ($100 \mu\text{g ml}^{-1}$, 30 min). The light-scattering on the outer surface of the zona pellucida has disappeared. Dark field, $\times 380$.

Fig. 4 An unfertilized egg pretreated for 30 min with wheat germ agglutinin ($100 \mu\text{g ml}^{-1}$), and then exposed to a 0.01% trypsin solution for 30 min. The inner region of the zona pellucida has been dissolved by the action of trypsin, but the outer region of the zona pellucida remains undissolved. Phase-contrast, $\times 380$.

Fig. 5 An unfertilized egg exposed to a 0.01% trypsin solution for 5 min without wheat germ agglutinin pretreatment, showing complete dissolution of the zona pellucida. Phase-contrast, $\times 380$.

Fig. 6 After pretreatment with wheat germ agglutinin ($250 \mu\text{g ml}^{-1}$, 30 min), an egg was inseminated with capacitated spermatozoa. Two hours later spermatozoa are colliding with the zona pellucida but fail to penetrate it. Phase-contrast, $\times 330$.

Fig. 7 Following pretreatment with wheat germ agglutinin ($50 \mu\text{g ml}^{-1}$, 30 min), an egg was inseminated with capacitated spermatozoa. Two hours later many spermatozoa are attached to the zona pellucida surface. Phase-contrast, $\times 330$.

Fig. 8 Egg treated as in Fig. 7, but the spermatozoa (except for one at 10 o'clock) on the zona pellucida have been removed by agitation. There is no indication of sperm penetration into/through the zona pellucida. Phase-contrast, $\times 380$.

Fig. 9 An egg (without wheat germ agglutinin pretreatment) was inseminated with capacitated spermatozoa. Two hours later the egg shows heavy sperm penetration. Arrows indicate swelling sperm heads within the egg cytoplasm. Phase-contrast, $\times 900$.

tration ($5 \mu\text{g ml}^{-1}$), but not at higher concentrations. If NAGlCA is present during the WGA treatment, the outer region of the ZP does not become resistant to trypsin dissolution. WGA also prevents β -mercaptoethanol from dissolving the outer region of the ZP at WGA incubation concentrations above $50 \mu\text{g ml}^{-1}$. This effect is also reversible at a low WGA incubation concentration ($50 \mu\text{g ml}^{-1}$) (Table 1), and can be completely blocked by NAGlCA if it is present during the WGA incubation.

Egg Fertilization

Fertilization of eggs is blocked by WGA (Table 1). When eggs are exposed to WGA, washed and inseminated *in vitro* with capacitated spermatozoa, these fail to penetrate through the ZP. Spermatozoa are unable to make permanent attachment to the ZP of eggs treated with very high concentrations of WGA ($>250 \mu\text{g ml}^{-1}$), although many spermatozoa constantly collide with the ZP surfaces (Fig. 6). When eggs are treated with lower WGA concentrations (50 – $100 \mu\text{g ml}^{-1}$), spermatozoa attach to the ZP surfaces (Fig. 7), but do not penetrate (Fig. 8). Untreated eggs, or eggs treated with very low concentrations of WGA ($<5 \mu\text{g ml}^{-1}$), show heavy penetration of spermatozoa through the ZP (Fig. 9). WGA inhibition of fertilization is reversible with NAGlCA when the eggs are treated with low WGA concentrations (10 – $50 \mu\text{g ml}^{-1}$) (Table 1). If NAGlCA is present during the WGA incubation, fertilization is not prevented.

These findings are similar to those of Shivers *et al.*²⁰, where it was found that rabbit antibodies against whole hamster ovaries block hamster fertilization. They identified the immunoglobulins responsible for the inhibition of sperm penetration as anti-ZP antibodies. These antibodies produced a precipitation layer on the outer region of the hamster ZP and prevented trypsin dissolution of the ZP²¹.

Our results indicate that WGA can block fertilization of hamster eggs by binding to oligosaccharides containing terminal NAGlCA in the outer region of the ZP. This region of the ZP may therefore be structurally different from the inner ZP region similar to the differences found between the inner and outer ZP regions of rabbit eggs²². Experiments with mechanically isolated hamster ZP indicate that the light-scattering optical properties associated with the specific binding of WGA are overwhelmingly localized in the outer ZP region and are not due to simple trapping or exclusion of WGA from the inner ZP region. (T. O., G. L. N., and R. Y., unpublished data). The loss of β -mercaptoethanol and protease susceptibility of the WGA-treated ZP could be due to steric masking of disulphide bonds and protease-sensitive polypeptide regions, or to allosteric changes in glycopeptide configurations that protect these sensitive bonds. A more likely possibility is that WGA does not prevent protease cleavage or disulphide reduction, but instead prevents the ZP matrix from dissolving by cross-linking oligosaccharide chains which are attached to adjacent polypeptides. If oligosaccharide cross-links are extensive, this could substitute an oligosaccharide-WGA ZP matrix for a disulphide-polypeptide matrix.

Treatment of hamster eggs with high concentrations of WGA ($>250 \mu\text{g ml}^{-1}$) prevents attachment of spermatozoa to the ZP. At saturating WGA concentrations, sperm receptors on the ZP may be sterically or allosterically blocked. Another possibility is that sperm-borne proteases are necessary for attachment and penetration, and the activity of these enzymes is blocked by ZP-bound WGA, but this must be reconciled with the ZP resistance to protease dissolution following treatment at concentrations of WGA that allow some sperm penetration through the ZP (Table 1).

In the hamster the ZP becomes impenetrable by spermatozoa in less than 15 min after entry of the first spermatozoon into the egg cytoplasm⁵. This change in the properties of the ZP, the "zona reaction"⁴, is thought to be induced by the

cortical granule material which is released from the egg cortex as a result of fertilization^{1,23}. Here it was found that WGA does not induce cortical granule breakdown; thus, the "zona reaction" is not involved in the prevention of sperm penetration by WGA. It is possible that the cortical granule material released after fertilization modifies the outer ZP region in a similar manner to WGA by steric masking of sperm receptor sites or by inducing allosteric changes in the glycopeptide matrix. As these changes are non-reversible, unlike the binding of WGA, it is probably more likely that the ZP is modified chemically by the cortical granule material.

The effect of WGA on hamster ZP does not appear to be a general property of phytoagglutinins, but instead is probably dependent on agglutinin saccharide specificity. Preliminary experiments with concanavalin A (specific for α -D-mannose-like residues)²⁴, *Ricinus communis* agglutinin (specific for β -D-galactose-like residues)²⁵ and *Dolichos biflorus* agglutinin (specific for N-acetyl-D-galactosamine-like residues)²⁶ indicate that concanavalin A does not entirely block hamster fertilization, but *R. communis* and *D. biflorus* agglutinins effectively block fertilization (T. O., G. L. N., and R. Y., unpublished observations). Concanavalin A sites are apparently more important on the egg surfaces of other species, such as the sea urchin *Paracentrotus lividus*, where it was found that concanavalin A ($100 \mu\text{g ml}^{-1}$) effectively blocks fertilization and egg cleavage²⁷. We are now studying the effects of different phytoagglutinins on fertilization and blastocyst implantation in the hamster and other mammalian species.

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LETTERS TO NATURE

PHYSICAL SCIENCES

Properties of the Radio Continuum Emission from Interacting Galaxies

SEVERAL interacting galaxies have been observed recently in different programmes using the Westerbork Synthesis Radio Telescope at 21 cm wavelength (beamwidth $24'' \times 24''$ cosec δ). We give here a compilation of the data in order to examine the morphology, strength, and the frequency of occurrence of the radio emission from these interacting systems.

than that of normal galaxies of similar optical magnitude. As a cautionary note, we mention that for the two systems which are common to our sample and that of Cameron, the higher angular resolution of our observations shows that unrelated nearby sources have caused Cameron to overestimate the flux densities of the systems themselves. Consideration of the number-flux density relation for radio sources leads us to believe that this confusion does not significantly affect the stronger sources in Cameron's sample, and that our conclusion is therefore still valid. A more precise statement must await the results of extensive high-resolution radio observations of galaxies now under way at Westerbork.

Table 1 Radio Emission from Interacting Galaxies

System	Other names	No. of members	Corrected total magnitude	Radio flux density $10^{-26} \text{ W m}^{-2} \text{ Hz}^{-1}$ at 1,415 MHz	Remarks
NGC 2444/45	VV117, Arp 143	2	11.7	0.020	Emission from the central HII complex in 2445
NGC 2798/99	Arp 283	2	11.7	0.072	Emission coextensive with 2798
VV150	Arp 322	4	13.7	0.025	Unresolved source in central galaxy
NGC 4038/39	VV245, Arp 244	2	10.2	0.212	Emission from dust patch between the galaxies
NGC 4438/35	VV188, Arp 120	2	9.5	0.060	Unresolved source in nucleus of 4438, and extended emission from dust patch of
NGC 4485/90	VV30, Arp 269	2	9.3	0.900 ⁵	Emission coextensive with 4490
NGC 4676A/B	VV224, Arp 242	2	13.1	0.027	Unresolved source in nucleus of 4676A
NGC 5194/95	VV1, M51	2	8.0	1.6	Spiral emission from M51, and weak emission from 5195 (ref. 6)
Stephan's Quintet	VV288, Arp 319	5	{ 11.7 —	0.027 0.040	Unresolved source in nucleus of 7319 Crescent shaped source between 7319 and 7318 ^{1,2}

There are nine interacting galaxy systems in our sample and for five of these the optical photographs show luminous bridges or tails. Radio emission from these features could have been resolved from that of the other parts of these systems; however, in no case was any emission detected in the bridges or tails. The origin of the delicate structures is controversial, and there are two main points of view. It has been variously suggested that they are the result of repulsive forces¹, and that magnetic fields are important in producing their ordered, filamentary structure². Recently, however, there have been successful attempts at explaining bridges and tails simply by gravitational tides during a close encounter of two galaxies^{3,4}. Our failure to detect radio emission from these bridges and tails supports the latter interpretation.

To determine whether the radio emission from other parts of these interacting galaxies is unusually intense, we have compared our data with the results of Cameron's survey of normal galaxies at 408 MHz (ref. 7). In Fig. 1, we plot the flux densities against the corrected total apparent magnitude both for the interacting galaxies and for the normal galaxies. For the interacting galaxies, these magnitudes are computed from values given by de Vaucouleurs⁸ or by Zwicky⁹ using the same method described by Cameron⁷. In plotting the interacting galaxies we have used a 1,415 MHz flux density scale which is displaced from the 408 MHz scale by assuming that the flux densities vary as (frequency)^{-0.75}. Normal galaxies at greater distances will extend the distribution in Fig. 1 along a 45° line towards the bottom left. It is clear that the interacting galaxies do not extend outside the region covered by normal galaxies; in particular, they do not extend above the rather well-defined upper boundary of the distribution. We therefore conclude that interacting galaxies in our sample do not emit significantly more powerful radio radiation

Purton and Wright¹⁰ have recently published the results of their independent study of four interacting systems which were previously known to be radio sources (of which three are common to our sample). They combined their observations at 4.6 and 2.2 cm wavelength (beamwidth 3.8 arc min and 2.1 arc min respectively) with lower frequency data and concluded that the radio luminosities and spectra of the interacting systems are similar to those of normal galaxies.

The preceding comparisons show that the interacting galaxies

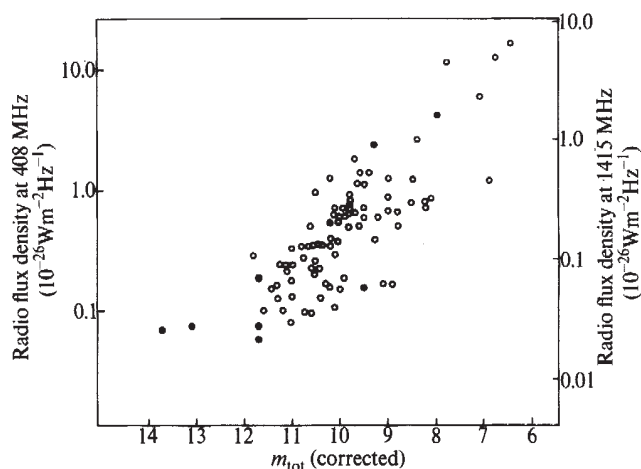


Fig. 1 Radio flux density versus total corrected apparent optical magnitude. $\circ$, Detected normal galaxies; $\bullet$, detected members of interacting systems. The 1,415 MHz flux density scale is displaced from the 408 MHz flux density scale by assuming a spectral index of -0.75 .

are not significantly stronger radio emitters than normal galaxies. We can further ask whether they are more frequent radio emitters. It is interesting that radio emission was detected in every interacting system observed; however, if we count the total number of galaxies in the systems we find nine detections out of twenty-one galaxies, omitting NGC 4485/90 because it was known from ref. 5. This number is not significantly higher than that found by Van der Kruit¹¹ (three out of ten) or by Cameron⁷ (92 out of 264). But it is difficult to draw a firm conclusion from these data without including effects of sensitivity and distance; this is hardly warranted until more extensive high-resolution surveys of normal galaxies are available.

We conclude that on the basis of the data presently available, most of the radio emission from systems of interacting galaxies can be accounted for both in frequency and intensity by the emission expected from the constituent galaxies themselves. This is further supported by the observation that the radio morphology of these systems is often similar to that of normal galaxies—either from the nucleus or coextensive with the optical image of a member galaxy. There are three interesting exceptions to this morphology in our sample; in NGC 4038/39, NGC 4438/35, and Stephan's Quintet¹², the present high-resolution observations reveal an unusual form of radio emission which is not centred on a member galaxy nor on any of the optical bridges or tails. It seems likely that in these cases at least part of the radio emission is a direct result of the physical interaction between members of the system.

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Radio Sources identified with Stellar Objects using Precise Radio and Optical Positions

It is difficult to establish the identification of a radio source with an object of stellar appearance and neutral colour. We show in this letter that such identifications can be made by comparing radio and optical positions of accuracy better than 1 arc sec.

Hoskins *et al.*¹ have produced a list of sources containing radio positions determined at 408 MHz together with the positions of nearby optical objects. The radio positions have

an accuracy of about 5 arc sec r.m.s. The optical positions were obtained from the Palomar Sky Survey prints, using the Molonglo two coordinate measuring machine and a technique similar to that described by Hunstead². Because of the radio errors the optical positions were quoted in ref. 1 to the nearest second of arc although their r.m.s. error is believed to be about 0.5 arc sec in each coordinate. The positions of all optical objects within about 45 arc sec of the radio position were measured and divided into two groups: those falling inside an error region whose limits were two standard errors from the radio position, and those outside this region. In order to estimate the background rate of occurrence of each class of object, randomly selected areas of the Sky Survey prints totalling approximately 385 (arc min)² were examined and all objects classified. As a result of these counts, an identification with either a blue stellar object (BSO) or a galaxy (g) fainter than 19 mag was claimed only for objects within the error region, but brighter galaxies were considered as possible identifications at displacements up to 20 arc sec. No identifications were claimed with stellar objects of neutral colour (St) because the number of such objects found within the error regions did not differ significantly from the chance expectation.

The interferometer of the Royal Radar Establishment (RRE) has been used to measure the positions of radio sources at 2,695 MHz with a typical accuracy of about 0.5 arc sec r.m.s. in each coordinate: these sources have radio angular extents less than about 10 arc sec. A first list of positions has been published³ and other lists are in preparation. There are 11 sources in these RRE lists which are common to the sources of ref. 1.

The common sources are biased towards flat radio spectra because the sources of ref. 1 do not appear in the 4C catalogue⁴ and are therefore generally weaker than 2 f.u. at 178 MHz, while the RRE sources are nearly all stronger than 0.4 f.u. at 2,695 MHz.

A comparison of the RRE positions with the positions of the optical objects noted in ref. 1 has led to some revision of the identifications in ref. 1. We give the revised identifications in Table 1: they are based on RRE accurate radio positions and Molonglo accurate optical positions. The description of the objects is taken from ref. 1. One of the 11 radio sources has a blank optical field; the remaining 10 are all identified with optical objects. Of the 8 identifications suggested in ref. 1, 6 are confirmed, including all 5 that were classified as BSO? or BSO. Two suggested galaxy identifications are not confirmed: the radio sources are now identified with a BSO? in one case and a stellar object in the other. In addition, two sources not previously identified have now been identified with stellar objects. The alterations occur chiefly because the more accurate radio measures make the position coincidences with stellar objects significant, whereas in ref. 1 stellar objects within the error regions could not be distinguished from chance associations.

The r.m.s. differences between radio and optical positions for the 9 stellar or possibly stellar identifications are 0.92 arc sec and 0.80 arc sec in right ascension and declination respectively. The mean differences, $+0.42 \pm 0.31$ and -0.18 ± 0.27 arc sec, are not significantly different from zero. The good agreement in position concerns the accuracy of the two sets of measurements, which were made completely independently. Following the definition in ref. 1, the error region for optical-radio position differences is an ellipse of semi-axes 1.8 and 1.6 arc sec. The counts quoted in ref. 1 show that the probability of finding a stellar object of neutral colour brighter than 20 mag in the combined error regions for the 11 sources one such region is only 1 in 50. Galaxies or BSOs brighter than 20 mag are even less frequent. These statistics give a high degree of confidence to the present identifications, whatever type of optical object is involved.

Ten sources out of the 11 have abnormal radio spectra

Table 1 Radio Source Positions and Optical-Radio Position Differences

Source (ref. 1)	RRE radio (1950.0)			Optical-radio			Identification	
	Right ascension	Declination		$\Delta\alpha$	$\Delta\alpha \cos \delta$	$\Delta\delta$	Object	Notes
1200+04.5	12 h 00 min 48.18 s	04° 31' 02.4"		+0.07 s	+1.0"	-1.7"	19 mag BSO?	2, 3
1355+01.0	13 55 20.44	01 01 08.0						4
1421+12.2	14 21 04.61	12 13 26.2		0.00	0.0	-0.4	18 St?	5, 6
1442+10.1	14 42 50.48	10 11 12.4		-0.07	-1.0	-0.6	18.5 St	7
1502+10.6	15 02 00.16	10 41 17.8		0.00	0.0	-0.3	18.5 BSO	2, 8
1555+00.1	15 55 17.68	00 06 43.1		+0.02	+0.3	-0.7	19 BSO?	5, 9
1616+06.3	16 16 36.52	06 20 13.8		+0.06	+0.9	+0.6	19 BSO	2, 5
1656+05.3	16 56 05.62	05 19 46.8		+0.03	+0.4	+0.2	17.5 St	10
1716+00.6	17 16 49.86	00 40 11.3		-0.20	-3.0	-0.4	20 g?	2
1743+17.3	17 43 22.27	17 21 08.5		-0.01	-0.1	+0.4	19.5 BSO	2, 11
1754+15.9	17 54 18.90	15 54 02.9		+0.16	+2.3	+0.9	18.5 BSO	2, 12

Symbols, as used in ref. 1.

g, Galaxy of unspecified type.

BSO, stellar image which is significantly brighter on the O ("blue") than on the E ("red") Sky Survey print.

St, Stellar image other than BSO.

? Indicates a doubt as to the nature of the object.

1. These sources appear also in other catalogues: for details see ref. 1.

2. Ref. 1 identification confirmed by RRE radio position.

3. The object may be a compact galaxy with a blue nucleus: it is stellar on the O plate and nebulous on the E plate. It lies in a faint cluster of galaxies.

4. Blank optical field.

5. RRE radio position from ref. 3, with right ascension reduced by 0.03 s to match AGK3 system.

6. St? lies in error region of ref. 1 but was not taken as an identification. Ref. 1 noted that the object is slightly blue and could be a BSO; re-examination of the Palomar Sky Survey confirmed that it is a BSO.

7. The present identification was first given by Véron^{9,10} who took the object to be blue. Our re-examination of the Sky Survey makes it neutral in colour.

8. This source has been identified by Blake⁶. It is a quasar with a redshift of 0.57 (Burbidge and Strittmatter⁸).

9. Ref. 1 identification with 19.5 mag phase g? lying in the error region not confirmed. BSO? lies outside the error region of ref. 1. The object may be a compact galaxy with a blue nucleus: it is stellar on the O plate and nebulous on the E plate. The present identification was first given by Véron⁹ using an RRE radio position.

10. St lies in error region of ref. 1, but was not taken as an identification.

11. Another 19.5 mag BSO lies 12 arc sec from the radio position¹.

12. Two other 18.5 mag BSOs lie 17 and 25 arc sec from the radio position¹.

(peaked, flat, inverted or complex). This is inherent in the selection and is also confirmed by measurements over a range of frequencies (H. S. M. and D. G. H., in preparation). Only the source 1716+00.6 has a normal spectrum (spectral index -0.8) and this is the only source identified with a galaxy. It appears in the present sample only because it occurs in a region where the 4C survey is obscured. The optical-radio difference in right ascension of -3.0 arc sec is significant in terms of the r.m.s. differences given above, and suggests a real separation between the optical and radio centroids of this source.

Of the 10 sources with abnormal radio spectra, 1 has a blank optical field and 9 are identified with optical objects. The Palomar Sky Survey images of these 9 objects were re-examined to check the type of those considered uncertain in ref. 1. The results of this examination are given in the notes to Table 1: the only definite change is that 1421+12.2 is classified as a BSO rather than an St?. The two sources classified as BSO? may be galaxies, but this is uncertain. (Identification of 1555+00.1 is of interest because the radio source has been shown by very long baseline interferometry⁵ to have most of its flux density in a component less than 0.0004 arc sec in extent: it has an inverted spectrum at low frequency possibly peaking between 5 and 10 GHz). The 10 sources thus comprise one blank field, 5 BSO, 2 stellar objects of neutral colour and 2 BSO? which may possibly be galaxies. The proportion of identifications with blue or neutral stellar objects (90% or possibly 70%) is much larger than the proportion found in samples of radio sources selected without regard to spectrum. Blake⁶ and Fanaroff and Blake⁷ have reported a similarly high identification rate with known or suspected quasars for sources with similar radio spectra to those discussed here.

The most interesting identifications are those of 1442+10.1 and 1656+05.3 with stellar objects of neutral colour. Confirmation of the nature of these objects would be highly desirable: they might, for instance, be quasars of high redshift.

The present work shows that stellar objects of neutral colour cannot be ignored as possible identifications with radio sources, and that radio and optical positions both accurate to better than 1 arc sec can produce such identifications. With combined radio and optical errors of about 5 arc sec, agreement in position is likely to be due to chance unless the radio spectrum is abnormal, in which case the probability of a genuine identification is greatly enhanced.

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Relativistic Behaviour of Circumnavigating Clocks

CONSIDERABLE interest has been aroused by Hafele's suggestion^{1,2}, subsequently supported by experiment³, that caesium beam clocks, borne by commercial jets circumnavigating the Earth, may provide supporting evidence for the famous prediction of Einstein's theory of relativity that if one member of a set of twins departs from the Earth in a spacecraft and later returns to reunite with his sibling, he will be the younger of the two. Strictly speaking, this statement is valid only if the frame of reference in which the home-bound sibling remains at rest is an inertial frame, which is not true of a frame of reference attached to the (rotating) Earth. This fact was ordinarily disregarded because the relative velocities involved were supposed to be much larger than the velocity difference caused by this circumstance. But in the case of clocks employed by Hafele and Keating³, this supposition is not true and the influence of Earth's rotation must be reckoned with.

In Hafele's calculation^{1,2}, a nonrotating frame of reference embedded in the Schwarzschild metric of the Earth played an intermediate role. Of course, the final result was expressed in terms of the ground speed of the flying clock. For flights confined to circular orbits in the equatorial plane, Hafele showed that

$$(d\tau/d\tau_0) \simeq 1 + gh/c^2 - (2\Omega Ru + u^2)/2c^2 \quad (1)$$

where $g = GM/R^2 - \Omega^2 R$ and M , R and Ω are the mass, the radius and the angular velocity of the Earth. Equation (1) contains a directional effect which arises from the term linear in u (u positive for eastward flights, negative for westward) and is related to the fact that the speed u is measured in a rotating frame of reference. This seems to have been overlooked by Schlegel⁴ when he suggested that the 'directional effect' appearing in equation (1) may be erroneous. Here, I present a calculation, made directly in the rotating frame of reference, which not only vindicates Hafele's result but also generalizes it to more practical situations.

In an arbitrary frame of reference, the space-time metric is

$$ds^2 = g_{ik} dx^i dx^k \quad (2)$$

where $x^i \equiv (x^\alpha, ct)$; $\alpha = 1, 2, 3$. The metric tensor g_{ik} includes the effects of gravitation as well as of the noninertial nature of the frame of reference. The proper time of a standard clock is then given by⁵

$$d\tau = dt [-g_{44} - 2g_{u4} (u^u/c) - g_{u\beta} (u^\beta u^u/c^2)]^{1/2} \quad (3)$$

where $u^\alpha = (dx^\alpha/dt)$. For a clock at rest, equation (3) reduces to

$$d\tau = dt (-g_{44})^{1/2} \simeq dt(1 + \Phi/c^2) \quad (3a)$$

where Φ is the Newtonian potential at the position of the clock. In a Lorentz frame, this becomes

$$d\tau = dt(1 - u^2/c^2)^{1/2} \quad (3b)$$

Now, if the underlying metric is of the Schwarzschild type (arising from the mass M of the Earth) and is viewed from a frame of reference K which rotates, with angular velocity Ω , with respect to the system of "fixed" stars, then the nonvanishing elements of the metric tensor, in the spherical coordinates (r, θ, ϕ) , are given by⁶

$$\left. \begin{aligned} g_{11} &= \left(1 - \frac{2GM}{c^2 r}\right)^{-1}, \quad g_{22} = r^2, \quad g_{33} = r^2 \sin^2 \theta \\ g_{44} &= \left(1 - \frac{2GM}{c^2 r} - \frac{\Omega^2 r^2 \sin^2 \theta}{c^2}\right), \quad g_{34} = g_{43} = \frac{\Omega r^2 \sin^2 \theta}{c} \end{aligned} \right\} \quad (4)$$

Substituting (4) into (3), and for slow motions ($u \ll c$) and weak fields ($\Phi \ll c^2$),

$$d\tau \simeq dt \left[1 - \left(\frac{GM}{c^2 r} + \frac{\Omega^2 r^2 \sin^2 \theta}{2c^2} \right) - \left(\frac{2\Omega r^2 \sin^2 \theta (d\phi/dt) + u^2}{2c^2} \right) \right] \quad (5)$$

In comparing the rates of two given clocks, the coordinate differential dt is eliminated.

Equation (5) contains two effects: the effect of altitude which, for $r = R + h$ ($h \ll R$), takes the form gh/c^2 where $g \equiv (GM/R^2 - \Omega^2 R \sin^2 \theta)$ is the "measured" value of the acceleration due to gravity at a place of colatitude θ ; and the effect of motion of the clock which is directional, because of the occurrence of the product $\Omega(d\phi/dt)$, and for $\theta = 90^\circ$ reduces to the Hafele expression $-(2\Omega Ru + u^2)/2c^2$.

Equation (5) may be applied to a satellite-borne clock as well. I consider motion in a circular orbit, of radius R^* , inclined at an angle λ to the equatorial plane of the Earth. Measuring ϕ from the line of nodes, in frame K

$$\theta = \cos^{-1}(\sin \lambda \sin \alpha), \quad \phi = \tan^{-1}(\cos \lambda \tan \alpha) - \Omega t$$

where angle α locates the satellite in its own plane of rotation: $\dot{\alpha} \equiv \omega = \sqrt{GM/R^*}$. Equation (5) then gives

$$d\tau^* \simeq dt(1 - 3GM/2c^2 R^*) \quad (6)$$

which is independent of λ and Ω , and depends only on R^* . In K_0 one would have

$$d\tau^* \simeq dt(1 + \Phi/c^2 - u^2/2c^2)$$

which, for $\Phi = -GM/R^*$ and $u^2 = \omega^2 R^{*2} = GM/R^*$, would again lead to equation (6).

Finally, comparing the satellite-borne clock with an Earth-bound clock (for which $\Phi = -GM/R$ and $u = 0$),

$$(d\tau^*/d\tau_E) \simeq 1 - (GM/2c^2)(3/R^* - 2/R) \quad (7)$$

the Ω -term is now clearly negligible. Effects predicted by equation (7) are about 100 times larger than the ones encountered in the case of jet-borne clocks. Establishment of Skylab may subject these effects to a more decisive test.

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Large Window Spectracon

IN the Spectracon¹ electronographic image tube, in the form now used for spectrographic recording, the image area is restricted to a rectangle 30 mm × 5 mm to enable a very thin (4 μm) mica Lenard window to be used which will support not only atmospheric pressure but also the pressure required to keep the electron-sensitive emulsion in intimate contact with the external mica surface when recording the image electrons.

Experience with this first type of tube has shown the high sensitivity of the device and high quality of the recorded images with excellent image definition, almost zero fog background, linear relationship of density with exposure and wide spectral range of sensitivity, thus making the tube very effective also for stellar photometry and the discrimination of faint objects against sky background. These possibilities were clearly shown by the work on stellar photometry by Walker². This work also showed clearly the great advantage that would be gained if the effective window area could be substantially increased.

For some time Spectracons with mica windows 25 mm × 10 mm have been made and used successfully³. As the tube has unity electron image magnification, the photocathode must be of the same dimensions as the window and hence a photocathode plate 10 mm wide must be transferred into the tube and the transfer tube sealed off under vacuum without damaging the photocathode.

To make a tube with a substantially larger mica window, say, 25 mm × 20 mm, required also a photocathode of the same dimensions. Trials with mica windows 25 mm × 20 mm and ≈ 4 μm thick showed that these were surprisingly reliable and stood up to combined atmospheric pressure and also the application of emulsion-coated film many hundred times without fracture.

Thus the strength of the mica window seemed adequate and the outstanding problem was to provide the photocathode of necessary area. To insert a photocathode plate of 20 mm width through a glass transfer tube and seal it off proved very difficult. Hence, as a compromise, photocathodes were prepared on two glass plates 30 mm × 10 mm lying side-by-side in an activation tube. In this way, there was practically no discontinuity in the photocathode sensitivity along the edges adjacent to one another. These two plates were then transferred to the Spectracon envelope with a 25 mm × 20 mm mica window through a standard 11 mm transfer tube by the technique already described and mounted with the same sides in contact in the photocathode mounting frame. It was found to be very important to mount these plates with their photo-

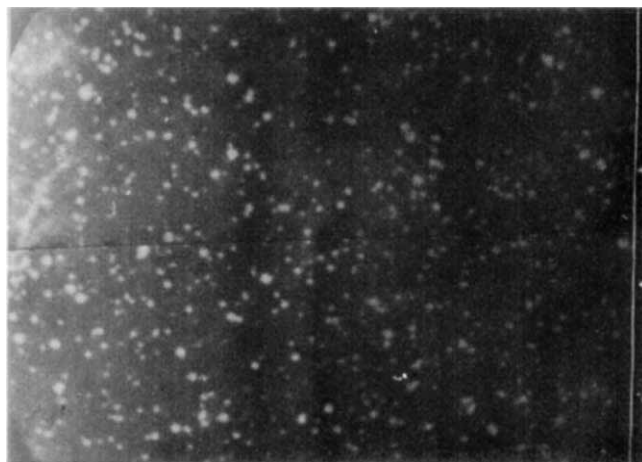


Fig. 2 Simulated star field picture reproduced by Spectracon (original size 25 × 20 mm²).

cathode surfaces accurately coplanar, otherwise electron-image distortion was serious.

Only minor modifications to the tube, film applicator and focusing solenoid were necessary to make and operate this tube, and hence the device is convenient for use at the prime focus of a telescope. It has now been under test and in use for six months and has proved to be very reliable. The image quality over the effective image area of 25 mm × 20 mm is substantially identical with that of the standard tube over its window area of 25 mm × 5 mm.

Fig. 1 shows a reproduction of a grid pattern used to test the geometrical accuracy of the electron image, and it can be seen that, for an image tube, this is exceptionally accurate. In Fig. 2 is reproduced a recording of a simulated star field, such as might be recorded at the prime focus of a telescope, and it shows that the image quality is comparable with that of a standard tube. The discontinuity across the picture where the two photocathode plates join is clearly visible but is considered to be a small penalty to pay for the increase by a factor of more than four in the effective image area. A process for eliminating this is now being investigated.

It is not practicable to show in a reproduced photograph experimental evidence of the limiting resolution of this tube, but careful tests show that it is ≥ 70 l. p/mm over substantially the whole area shown in Figs. 1 and 2.

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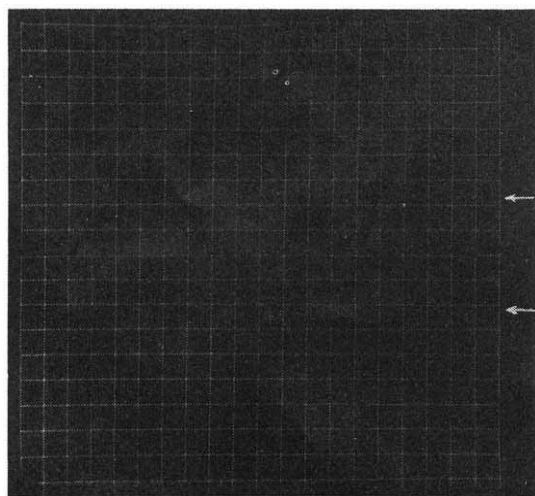


Fig. 1 Rectangular grid pattern 22 mm × 20 mm recorded by Spectracon. Arrows indicate effective width of window of "standard" Spectracon.

Allende Meteorite Carbonaceous Phase: Intractable Nature and Scanning Electron Morphology

METEORITES, being solar nebula condensates¹, should carry information on the processes which led to formation of the planets. Within this context Green, Radcliffe and Heuer² studied 1 μm thick foils of the Allende C-3 chondrite by means of high voltage transmission electron microscopy (TEM). Its chondrules (small silicate spheres) showed features which

suggested that they were older than the microcrystalline matrix which alone contained carbon. If the matrix crystallized directly from the circumstellar plasma as virgin planetary material³ further study of its carbon phase would be of interest because little is known of the nature of the insoluble carbonaceous "polymers" of meteorites⁴. The Allende chondrite contains about 0.3% carbon of which 100 p.p.m., extractable by organic solvents, has been extensively studied⁵. The origin of this organic matter is an extremely controversial subject⁶.

We have examined the ultrastructure of the Allende matrix by scanning electron microscopy (SEM) and isolated the carbonaceous phase for study by mass spectrometry and oxidative thermal analysis. SEM sample preparation consists of vacuum-deposition coating with conductive Au-Pd film a few angstroms thick. This was augmented by selectively etching the silicate matrix with gaseous fluorine generated in a Model IPC 1003B microwave plasma generator^{7,8} supplied by International Plasma Corp., Hayward, California. SEM thus complements TEM by establishing the size range, three-dimensional appearance and shapes and types of particle arrays in the matrix. Energy-dispersive X-ray spectroscopy was used to determine the composition of μm -size areas for elements

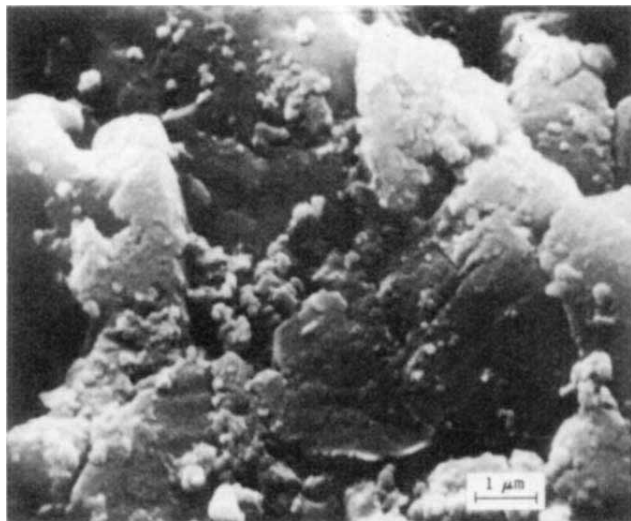


Fig. 1 Scanning electron micrograph of fresh Allende matrix fracture surface. Carbon aggregates and films which cover many areas in the central portion of the picture are seen by comparison with Fig. 2.

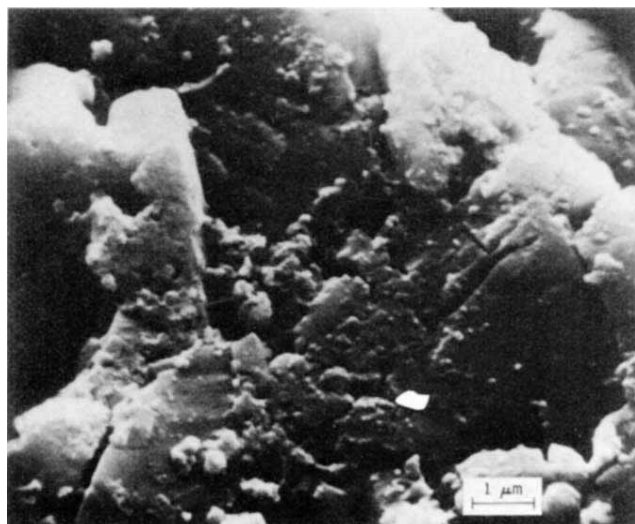


Fig. 2 Same area shown in Fig. 1 after exposure to plasma oxygen which has removed all carbon elements and consequently left prominent cracks exposed in several matrix crystals.

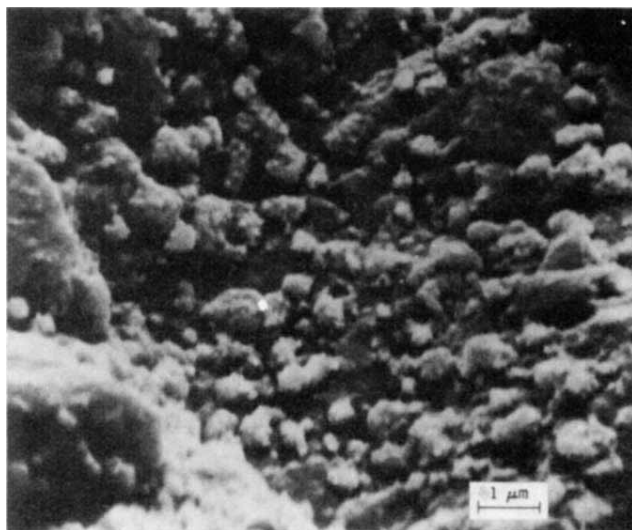


Fig. 3 A similar matrix fracture surface with numerous rounded microspherical carbon aggregates exposed by fluorine removal of the silicates.

heavier than sodium. The Allende chondrite used in this study was specimen 818 from the Center for Meteorite Studies, Arizona State University at Tempe.

An SEM view of an Allende matrix fracture surface (Fig. 1) contrasts sharply with that shown by TEM (ref. 2); it appears as a polymict breccia of randomly oriented forms some of which are anhedral. The grains are coated with a sodium-calcium rich glass and carbon occurs at the grain boundaries as irregular microspherical aggregates 1–3 μm in size, frequently with similar silicate forms. These carbonaceous areas give no response to energy-dispersed X-rays and they are quickly destroyed by plasma oxygen⁹ (Fig. 2). Careful comparison of fresh and plasma oxygenated surfaces (Figs. 1 and 2, respectively) shows that the matrix also contains carbon as a surficial film about 0.1 μm thick which coats matrix grains but does not fill their surface interstices.

Exposure of a fracture surface to fluorine for an arbitrary period of 14 h (Fig. 3) exposes the carbon aggregates and clearly shows that they occur at former grain boundaries in roughly linear arrays. When the carbon is removed by exposure to plasma oxygen the fluorine has etched the silicate grains in such a way that they are also shown to be comprised of microspherical phases. These are seemingly identical morphologically to the subsolidus "liquid-crystalline" phases of feldspars described by Greer¹⁰. The carbonaceous aggregates vary from about 0.5 to 3 μm in size and are comprised of featureless spherical subunits about 0.05 to 0.2 μm in diameter. The "disordered graphite" area described by Green *et al.*² seems to be a cross-sectioned aggregate in which the spherical subunits appear as dark pinpoints.

The random (non-regularly packed) clustering of featureless carbon and silicate microspheres into irregular aggregates argues for their vapour phase growth in free space, with little interparticle interaction¹¹. The mode of origin is not clear from morphology alone; they may have formed by *in situ* surface reactions on the matrix grains^{12,13}. The size distribution and composition of the matrix also correspond to those postulated for interstellar dust^{14,15}, possibly trapped during nebular collapse.

Nearly identical carbon aggregates form from the liquidus mesophase of polycyclic aromatic hydrocarbons pyrolysed within very narrow temperature ranges at pressures of 1–30 kbar (refs. 16, 17). By analogy, the morphology of the Allende carbon and silicate microspherical aggregates suggests formation under high-pressure transient heating (and quenching), possibly as shock fronts displaced the asphalt threshold¹⁸ within the unstable nebular cloud. These observations strongly

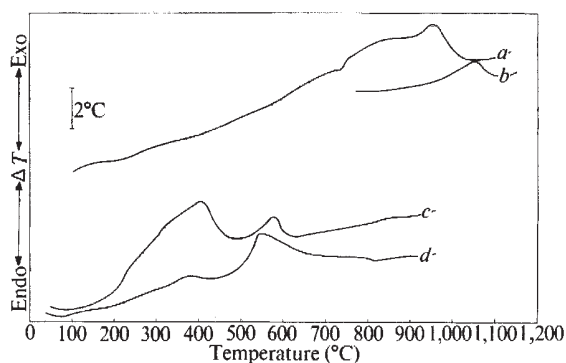


Fig. 4 Differential thermograms in an oxygen atmosphere: *a*, used Fischer-Tropsch iron catalyst; *b*, crystalline graphite, Essex Co., New York; *c*, Allende chondrite HF digest carbon phase, about 7.5% carbon; *d*, Allende chondrite ground to a particle size of about 100 μm .

support the theory of Arrhenius and Alfvén³ that primordial solar condensation took place by gas accretion.

Gaseous fluorine also causes sellaite (MgF_2) artefact aggregates to form on surfaces of peridot (olivine) ($\text{Mg,Fe})_2\text{SiO}_4$ and magnesium silicate glasses but these are not confined to grain boundaries and are removed readily by boric or sulphuric acids. Carbon aggregates are never formed on minerals etched with the CF_4 microwave plasma decomposition products. The "temperature" of the plasma, about 40–100°C, is insufficient to fluorinate carbon destructively¹⁹. The silicate microspherical aggregates also appeared when the matrix was etched with the "olivine-specific" etchant of Krishnaswami *et al.*²⁰; they may be precipitates within grains, as noted by Green *et al.*².

An SEM examination of used Fischer-Tropsch catalyst showed its surface to be sparsely coated with carbonaceous aggregates nearly identical to those of the Allende meteorite. The sample, provided by Martin H. Studier, was Canyon Diablo siderite baked at 900°C and used to catalyse a "1:1 mixture of H_2 and CO for several days at 200°C"; its composition was C 0.66%, H 0.29% and N 0.0%. Studier, Hayatsu and Anders²¹ have suggested that Fischer-Tropsch reactions may be sources of meteorite organic matter and this observation does not contradict that hypothesis.

A carbonaceous phase concentrate was prepared from the Allende stone by treatment with cold excess hydrofluoric acid (48%). The black partly gelatinous digest was taken up in dry acetone after being washed to neutrality with water; it was further dried by addition of 2,2-dimethoxy-propane and finally taken up in dry acetone alone. An aliquot determination of the final slurry showed 55.7% recovery of starting material. After crushing in an agate mortar to reduce undissolved chondrules the slurry was applied to a gradient column of acetone, chlorobenzene, chloroform, methyl iodide and bromoform²². The carbonaceous phase remained in the acetone from which it was recovered as a black powder with a composition of C 7.45%, H 1.36% and N 0.02%, or essentially as CH_2 "polymer". X-ray diffraction showed only sellaite (MgF_2) and an amorphous solid and its SEM appearance was identical to that of the microspherical aggregates exposed by fluorine on meteorite fracture surfaces.

The concentrate was insoluble in common organic solvents, in the equivolume mixture of nitrogen tetroxide-dimethylformamide which dissolves linear ionic polymers (and cellulose)²³ and in liquid ammonia at 25°C (ref. 24). Simon's reagent ($\text{Ag}_2\text{Cr}_2\text{O}_7$ in H_2SO_4) (ref. 25) attacked it at a rate 1.7 times less rapidly than graphite and it was unaffected by concentrated aqua regia at room temperature. Only traces of (principally) substituted benzenes were evolved when it was heated through 600°C in the solid inlet probe of an electron-impact mass spectrometer in complete agreement with the findings of Muenow, Steck and Margrave²⁶ who heated the whole chondrite through 1,500°C in a Knudsen cell within a mass spectrometer. Hayes and Biemann²⁷ reported similar

results for the Murray and Holbrook chondrites. Spark source mass spectrometry²⁸ of the concentrate showed no cracking patterns for graphite²⁹, although numerous mass peaks for procedurally enhanced Mg and Ba fluorides and rare earths were present. The carbonaceous phase of the Allende chondrite is thus not a classical linear polymer nor graphitic.

Confirmation of its non-graphitic nature was provided by differential thermal analysis (DTA) in oxygen. DTA applied to coals and other kerogens³⁰ "ranks" them in terms of their peak exotherm temperatures which increase with diagenetically induced "fixed carbon" (graphite) content. By analogy, other complex systems can be similarly ranked and this has been done for the Allende, Mighei, Kainsaz and Grosnaja chondrites⁴.

The present study was carried out at a very rapid nonlinear heating rate in flowing oxygen. A ballistic programme with a nearly linear rate of 80°C min⁻¹ up to 600°C, which gradually decreased to 15°C min⁻¹ at 1,000°C was obtained by applying full power to an 'R. L. Stone' 1,400°C platinum wound furnace which contained an 'R. L. Stone Series 11' open pan thermal head and a chromel-alumel ring thermocouple. A third connexion to the centre of the thermocouple permitted recording on the temperature axis of a DuPont 990 thermal analyser. Pure oxygen was swept through the system at 70 ml. min⁻¹ to emphasize exothermic reactions. The DTA portion of this study, which included that of a number of other chondrites, will be discussed elsewhere.

The DTA results (Fig. 4) indicate that the Allende carbonaceous component is nongraphitic and that of the used F-T catalyst is similar to graphite. Reduced iron F-T catalysts are coated after use with hydrocarbon waxes and Hägg (Fe_2C) and other complex carbides³¹ so that interpretation of this DTA data must await study. The rate of the F-T reaction which is, however, strongly pressure dependent would be vanishingly small in space except possibly under transient high pressure conditions (R. B. Anderson, personal communication). The two exotherms in the DTA data confirm the SEM observation that two forms of carbon are present in the meteorite. Comparison exotherms (°C) under these exact conditions are: (coals)—lignite 480, bituminous 555, anthracite 650, meta-anthracite 705 and graphite 800–1,060°C depending on degree of crystallinity. An attempt to isolate "Allende aggregates" from cellulase digests of filters flown through the debris cloud³² was unsuccessful.

The morphology of the Allende matrix and its carbon phase revealed in this study suggests that the meteorite was formed by condensation from the gas phase in a complex series of events¹. The nature of the non-graphitic carbonaceous phase is not clear although its intractable solvent properties and thermal stability suggest that it is not a polymer in the classical sense. Tamaru³³ has suggested that it may be an intercalation complex of amorphous carbon. Such sandwich complexes possess variable stoichiometry but those of graphite are regular, as for example K_8C . An investigation is in progress to determine the stoichiometry of the reaction product of the Allende carbonaceous phase and potassium in order to test this hypothesis.

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Saharan Glaciation Dated in North America

THE Lower Palaeozoic glaciation in the Sahara is rapidly becoming among the best known of fossil glaciations¹⁻³ but because rocks within and below the glacial sequence are poorly fossiliferous it has proved difficult to estimate the duration of glacial conditions. We suggest that the duration of the glacial episode is dated as extending from Lower Cambrian to Middle and perhaps Upper Ordovician by the

occurrence in eastern North America of resedimented deposits indicating widespread simultaneous development of submarine canyons in response to glacio-eustatic lowering of sea level.

Eustatic sea level changes are chiefly responses to changes in the total volume of the mid-ocean ridge⁴ and as such are controlled by spreading rate changes and changes in ridge length. These changes perhaps result from competition among mantle plumes⁵. Significant changes in sea level resulting from changes in ridge volume take place over periods of the order of 10⁶ yr (ref. 4) and sedimentary processes governed by base level have little difficulty in adapting gradually to them. By contrast, glacially controlled eustatic changes take place over periods of less than 10⁴ yr and produce sudden changes in base level. Daly⁶ pointed out that glacial lowering of sea level greatly enhances submarine canyon activity and examples of canyon development related to the late Würm-Wisconsin low stand are widely reported (see for example ref. 7). We therefore suggest that a sudden onset of intense submarine canyon development recorded within a sedimentary sequence may be an indication that glaciation has started elsewhere. The criterion has to be applied cautiously because submarine canyons develop for a variety of reasons in tectonically active areas (for example in the Mediterranean⁸). Canyon deposits in the Late Permian of New Zealand are contemporaneous with a Late Permian glacial episode^{9,10} but cannot be entirely dissociated from possible seafloor disturbance because they occur among thick marine deposits on the leading edge of a plate. The least ambiguous indications of glaciation beyond the ice-covered region are to be sought in miogeoclinal marine sequences with little contemporary tectonism. In contrast to tectonically controlled canyons glacio-eustatic canyons must start to develop at the same time all over the world. Final proof of the origin of a particular set of canyons comes by demonstrating both intercontemporaneity and contemporaneity with onset of glaciation. This has been achieved so far only for the Pleistocene and to some degree for the Permian. It should be possible to apply the same technique to the newly discovered Lower Palaeozoic glaciations because contemporary miogeoclinal wedges are widely reported.

The North American continental margin of the Proto-Atlantic Ocean during much of the Cambrian and Lower to Middle Ordovician was a carbonate shelf rather like the Sahul shelf north of Australia today¹¹. Shelf limestones outcrop from Alabama to Newfoundland as well as in Greenland and Scotland over a minimum distance of 6,500 km (ref. 12). Because most coarse material resedimented from modern stable continental shelves passes down submarine canyons¹³ we interpret major occurrences of coarse resedimented material down slope of the Cambro-Ordovician shelf break as evidence of submarine canyon activity and hence in this tectonically inactive environment of glacial events.

Comprehensive analysis of the age distribution of resedimented units must await refinement of Appalachian stratigraphy. As an example of the kind of analysis which

Table 1 Sedimentary Carbonate Breccias (XXX) Occurring at Ten Localities along 2,000 km of Strike in the Northern Appalachians

Ages	Frederick (Maryland)	Lancaster County (Pennsylvania)	Near Albany (N.Y.) in Taconic Klippe	Milton (N.W. Vermont)	Quebec (Levis P.Q.)	St. Jean Port-Joli (Gaspé P.Q.)	St. Fabien (Gaspé P.Q.)	Cow Head (Nfld.)	Humber Arm (Nfld.)	Hare Bay (Nfld.)
Middle Ordovician			XXX		XXX			XXX		
Lower Ordovician	XXX			XXX	XXX		XXX	XXX		
Upper Cambrian	XXX			XXX	XXX			XXX		XXX
Middle Cambrian		XXX		XXX	XXX			XXX	XXX	
Lower Cambrian		XXX		XXX		XXX				
Reference s	12	11	12	11	12	18	18	12	12	12
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can be made at present we have set down (Table 1) the age distribution of coarse, resedimented, carbonate breccias at 10 localities in the Northern Appalachians. Episodes of resedimentation occurred from soon after the inception of the miogeocline in Lower Cambrian times to the changes in sedimentary polarity marking the development of tectonic lands to the south-east in Middle and Upper Ordovician times¹⁴. From this we infer that glacial conditions prevailed intermittently somewhere in the world from Lower Cambrian times to Upper Ordovician times. The western Sahara was polar throughout this time¹⁵ and although most of the well preserved glacial deposits are Caradocian to latest Ordovician in age there is a record of Early Cambrian glacial deposits from Colomb Bechar¹⁶ and there are widespread Eo-Cambrian glacial deposits in the western Sahara¹⁷. The incompleteness of the earlier record is not surprising because successive continental glaciations in the same area cannibalize sediments so that only the latest episode leaves a substantial record. Whether or not there was continuity from a widespread Late-Precambrian glacial event cannot be demonstrated on evidence from eastern North America because the miogeocline had not developed during the critical interval.

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Elemental Carbon in Marine Sediments: a Baseline for Burning

A RECORD of prehistoric and historic burning of carbonaceous materials may be found in the elemental carbon contents of the sedimentary columns. The widespread dissemination of such carbon as microcrystalline graphite is indicated by its presence in atmospheric dusts collected over the North Atlantic¹ and in ice nuclei collected from North Pacific airs². Its submarine survival over geologic time periods, at least up to millions of years, is suggested by its occurrence in manganese nodules³ and in sediments from the Sierra Leone Rise¹. But a biologically mediated oxidation of elemental carbon in terrestrial soils has been proposed to explain the gradual disappearance of charcoals originating from forest fires⁴. The

contributions of carbon from industrial activities are also visible and well documented (see, for example, ref. 5).

Prehistorically, the production of elemental carbon has been associated with the high temperature burning of plants and plant remains and in the formation of coal. Recent evidence⁶ suggests that all ranks of coal from lignite to anthracite can be produced at temperatures below 200° C. There is an additional source from coal, oil or gas burning by human society. In energy production, depending upon the nature of the combustion process, it can achieve levels of around 5% in the residue⁷. Coal burning produces a variety of solids including magnetite, haematite, quartz and mullite. The latter mineral (3 Al₂O₃, 2 SiO₂) is rather rare in crustal materials; it occurs in pelitic xenoliths in basic igneous rocks⁸. In coal ashes it varies between 0 and 16%. It may be a useful diagnostic tracer of coal burning and a search for the mineral in atmospheric dusts and in sediments might prove rewarding.

The dispersion of elemental carbon introduced to the atmosphere may be followed by its fallout patterns in the slowly depositing open ocean sediments. Further, in sediments of known accumulation rate, the carbon fluxes can be ascertained; carbon may also prove to be a useful tracer for other materials mobilized through the atmosphere as a result of fossil fuel combustion⁹. We have, therefore, attempted to provide a set of background values of natural (not induced by man) burning processes.

The carbon analysis is carried out by infrared spectroscopy and is based upon the development of a characteristic spectrum of elemental carbon produced during a long term grinding process¹⁰. Infrared bands at 1,720, 1,580 and 1,240 cm⁻¹ are produced as a result of a high temperature and high pressure oxidation of the carbon surface during such grinding. Most elemental carbons, such as petroleum charcoal, lampblack, graphite, decolorizing carbon, and soot from oil or coal-fired furnaces, yield this spectrum. We chose petroleum charcoal as our standard substance because of its low ash content relative to the other carbons examined. We found that the absorbance of the 1,580 cm⁻¹ band is directly proportional to the mass of carbon in the sample.

Table 1 The Elemental Carbon Contents of Pelagic Sediments

Sample	Depth inter-val (cm)	Depth (m)	Latitude	Longitude	Carbon content* (wt. %)
Pacific					
LFGS 19G	0-10	2,799	57° 21' N	150° 47' W	0.090, 0.099
ANT 3 42P	0-5	2,386	56° 23' N	171° 04' E	0.098
Zts III 5G	4-15	4,714	45° 16' N	158° 10' E	0.051, 0.048
Zts III 4G	0-10	6,232	39° 30' N	170° 51' E	0.070
F/H 1a	0-10	5,700	39° 26' N	148° 48' W	0.060
Zts III 2G	0-10	5,773	37° 55' N	150° 32' E	0.082
Nova-A-1G	0-10	5,400	34° 23' N	146° 02' W	0.065
Scan 29 Pb	0-10	5,857	33° 16' N	153° 44' E	0.086
Scan 22P	0-10	3,862	32° 20' N	159° 15' E	0.024
Nova-A-2G	3-13	5,740	31° 35' N	166° 34' W	0.028
Zts VII 40G	0-15	5,050	30° 12' N	143° 17' W	0.070
Scan 21P	0-10	5,709	28° 59' N	168° 55' E	0.076
Nova-A-5G	3-13	5,894	25° 45' N	175° 53' E	0.037
LSD-H-101va	0-10	5,100	22° 08' N	139° 00' W	0.038
Scan P PGb	0-10	5,186	19° 56' N	139° 52' W	0.047
CRM 11G	0-15	5,820	16° 52' N	156° 47' E	0.032
7-Tow S					
K 1-5 FF	0-10	4,641	13° 46' N	126° 07' W	0.051, 0.049
Wah 6FF-2	0-10	4,787	6° 08' N	152° 38' W	0.015
Amph 133G	0-10	4,149	3° 32' S	141° 26' W	0.0047
Scan 78P	0-10	4,231	12° 15' S	134° 19' W	0.0056, 0.0055
Nova H 20G	0-10	3,063	12° 53' S	176° 39' E	0.0022
Scan 80G	0-10	4,697	24° 53' S	143° 27' W	0.0023
Nova-A-48G	0-13	2,220	28° 12' S	158° 13' E	0.00090
Msn 111G	0-15	5,230	40° 37' S	164° 08' W	0.027, 0.029
Atlantic					
Zeph-I-22G	0-12	5,601	25° 05' N	34° 13' W	0.029
Zeph-I-23G	0-10	5,209	26° 14' N	26° 27' W	0.020
LSD-A-216V	0-10	2,820	3° 18' N	31° 03' W	0.019

* Duplicate values were obtained through analyses of the same isolate. The values are indicative of the precision of the method.

A basic peroxide treatment of the gross sediments was sufficient to destroy a substantial portion of the organic matter without attacking the elemental carbon. This is a particularly important step because the spectra of some humic acids¹¹ are similar to that developed for carbon. Full details of our technique will be published later.

There is a marked increase in the carbon concentrations of pelagic sediments going from the southern equatorial regions northward (Table 1, Fig. 1). Clearly, normalizing the data to a time parameter (such as rates of accumulation) would be more reasonable. Because the more northerly deposits are more rapidly accumulating than their southern counterparts¹² the latitudinal differences in carbon accumulation per unit time would be even more dramatic. The carbon contents of the few Atlantic sediments analysed fit the general latitudinal dependence pattern of their Pacific counterparts. Because the rates of deposition of both groups are similar¹², this suggests that the same processes may be operative in bringing the carbon to the marine environment.

The most likely source of the carbon in these deposits (we have integrated over about the upper 15 cm of sediment, the past 100 m.y.; the top 0.5 cm, corresponding to the past 5,000 yr, was not included) is the debris produced in forest fires. Graphite may form during the thermal metamorphism of sedimentary rocks. But the observed latitudinal variations of carbon do not relate to the distributions of such materials and we did not pursue this possible source of carbon further. In Fig. 1 we have plotted the extent of four types of forest: conifer, non-coniferous temperate, Mediterranean, and tropical. If the burning hypothesis is correct, the primary contributors of carbon to the prehistoric sedimentary record are most probably the first three types of forests¹³.

There is in general a latitudinal zonation of forest types about the Earth's surface (Fig. 1). The forests are distinguished by the type and extent of their vegetation which in turn reflects differences in soil, climate, elevation and past land use. At higher latitudes, before the ice sheets are approached, the tundra is covered by mosses and lichens with only occasional small trees. Cool coniferous forests belt the Scandinavian countries, across Russia to Siberia and continue over much of Northern Canada. Their trees consist largely of spruce, pine, fir, hemlock and cedar with some birch and willow. Southward, they blend into the temperate mixed forests of the eastern United States, the British Isles, central Europe and eastern Asia.

The tropical forests span the near equatorial regions. In the Amazon basin, western and west-central Africa and in south-eastern Asia are high concentrations of these forests. The combustion of tropical forest organic matter is through low temperature biologically mediated processes without the production of carbon. In contrast to these rain forests are the drier open woodlands or savannas, which contain primarily grasses and only small numbers of trees.

The winds which can move the debris of high temperature burning from the continents to the ocean environment are zonal. The three chief systems in the lower atmosphere are the easterly trades of the equatorial regions which blow from east to west, the westerlies of the mid-latitudes, much more intense at higher elevations and more variable, and the polar easterlies of relatively low intensity and high variability. Particles injected at one latitude will normally travel along it with spreading to the north and south due to the meanderings of the flow patterns. The principal contributions to atmospheric dusts are from the arid regions of the world; maximum burdens, as seen in their deposition to the marine sediments, occur at around 20–30° N and 30–40° S (ref. 14). Their transport is in the prevailing westerlies which most probably are responsible for the dispersion of much of the carbon produced in forest fires.

The relative production of carbon particles by forest fire burning and by fossil fuel combustion may be estimated on the following basis. The US production of particulates from the combustion of fossil fuels from stationary sources has been

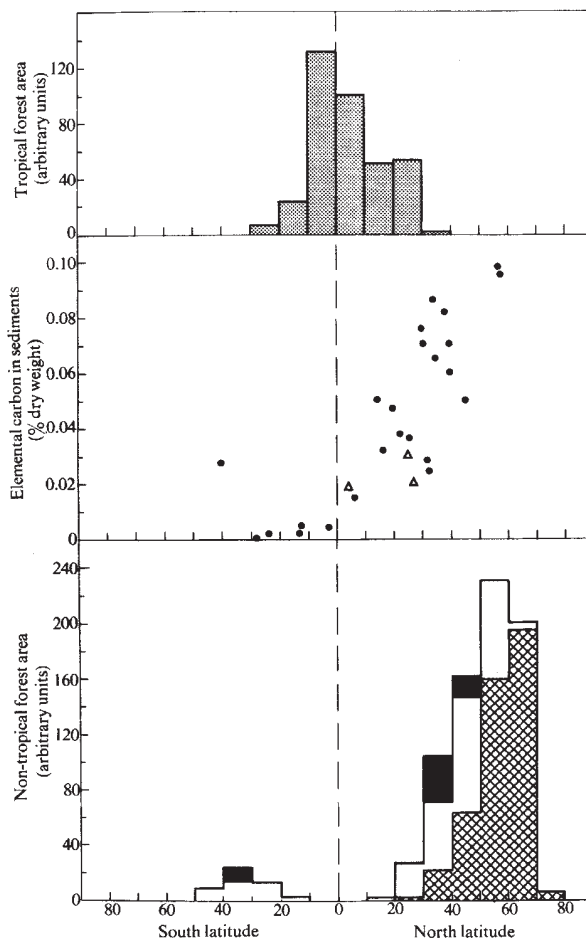


Fig. 1 The elemental carbon concentrations in Pacific deep-sea sediments as a function of latitude with the corresponding areal extents of forests¹⁹. In the lower histogram, the hatched areas represent conifer forests, the unshaded areas the non-coniferous temperate forests, and the black areas the Mediterranean forests. ●, Pacific; △, Atlantic.

estimated as 6 mtons yr⁻¹ (L. J. Shannon *et al.*, at 2nd International Clean Air Congress, Washington, 1970). A value for both stationary and moving sources of 10 mtons yr⁻¹ has been quoted¹⁵. We use the lower figure, multiplied by a factor of 3 to extrapolate it to a global value, to estimate conservatively the introduction of carbon to the environment. Further, we assume that 1% of these particulates is elemental carbon, that its disposition is uniform about the northern hemisphere, and that it is not degraded in the atmosphere. On such a basis there would be an annual fallout on land and sea of 0.07 $\mu\text{g cm}^{-2}$ of fossil-fuel generated carbon (a total of 0.18 mton).

Robinson and Robbins¹⁶ make a rough assessment of the contributions of forest fire particulates to the total atmospheric aerosol burden. Again, these particulates are not totally carbon. The US has an annual forest fire area of 4.5×10^6 acre. This expanse is taken to represent 25% of the global forest fire area, 18×10^6 acre. The average amount of fuel burnt per acre is assumed to be 18 ton or 90% of the wood growing in forested areas. The particulate emission for such burning is estimated to be 17 pound per ton giving, as a total global emission, 3×10^6 ton annually. If 10% of this is carbon (0.3 mton yr⁻¹ or 0.12 $\mu\text{g cm}^{-2}$ of the Earth's surface, if emissions are assumed to be confined to the northern hemisphere), the forest fires and energy production are now contributing comparable amounts of carbon.

Other estimates of the production of these forest fire particles cited by Robinson and Robbins range from 27 mton yr⁻¹ for the US alone with an addition of 17 mton yr⁻¹ from slash burning and forest litter control operations, to a global

particulate production of 150 mton yr^{-1} . This difference is not unexpected when the difficulties in dealing with such poorly defined numbers are taken into account.

The estimated elemental carbon emission from forest fires, $0.12 \mu\text{g cm}^{-2} \text{ yr}^{-1}$, seems to be in reasonable accord with the amounts which we have found in the North Pacific sediments. The rate of sedimentation for these deposits can be taken as 1 mm per thousand years¹². With an average carbon content of 0.05% (Fig. 1; Table 1), and a density of 2 g cm^{-3} , the rate of accumulation of carbon is $0.1 \mu\text{g cm}^{-2} \text{ yr}^{-1}$.

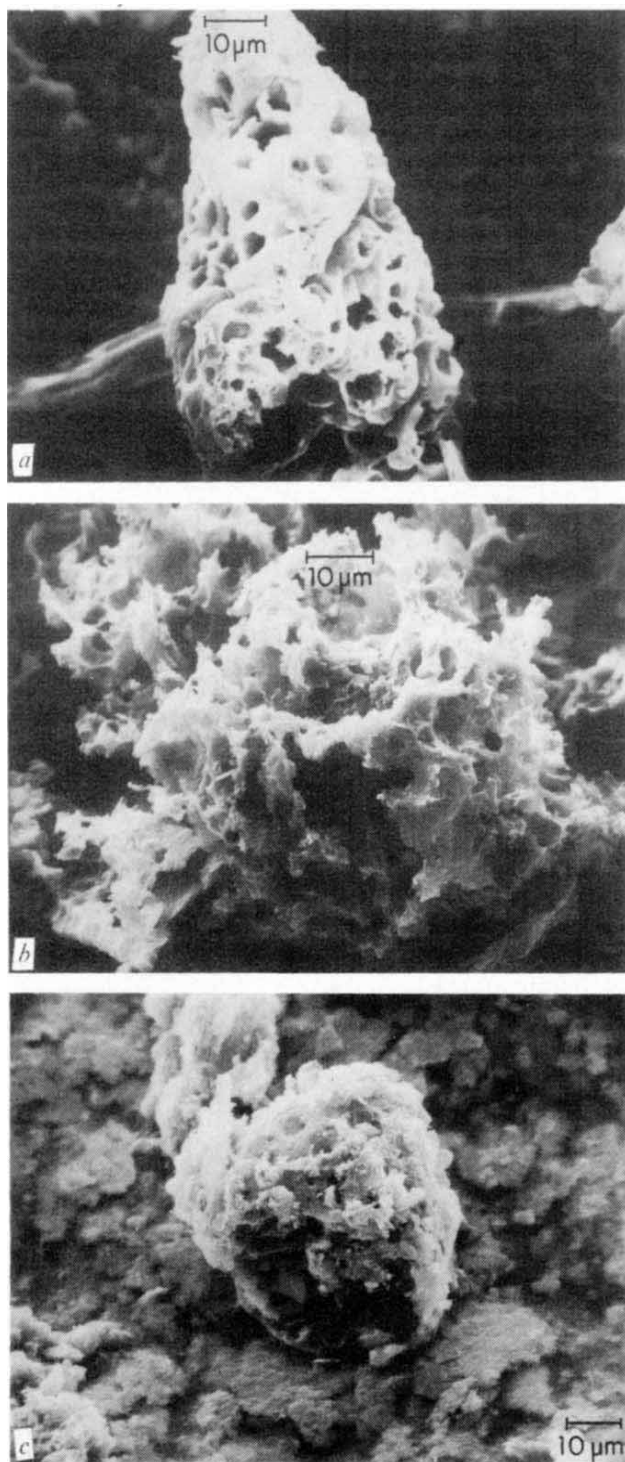


Fig. 2 a, Carbon particle isolated from forest fire particulates, San Diego County, Sample 56P; b, carbon particle from the chimney of a wood burning domestic fireplace; c, carbon particle isolated from Zts 40G.

Additional evidence that the carbon in these marine sediments has an origin in forest fires derives from scanning electron micrographs of carbon separates from flyash-containing sediments and atmospheric particulate matter collected downwind from a forest fire (Fig. 2). The forest fire occurred in the Julian-Poway-Ramona area, east of San Diego, on October 30, 1967 and the carbon particles were isolated from the bulk of the material by an HF-HCl treatment. The morphology of such particles is similar to those extracted from marine sediments. The larger carbon particles (diameter $>20 \mu\text{m}$) associated with forest fires and other wood burning (Fig. 2a and b) retain a morphology seemingly fashioned by the cellular structure of the wood¹⁸.

The carbon particles in the deep sea sediments had diameters usually no more than several microns. Because of their small size these particles did not show any cellular features of wood. Occasionally larger particles were encountered (Fig. 2c) and bore a striking resemblance to particles produced in wood burning. Scanning electron microscopic studies on the larger carbon isolates from the sedimentary column seem promising to complement and to extend palaeopalynological investigations concerned with the extent and types of forests in past geological times.

Such size distributions are similar to those of atmospheric particulates of continental origin collected over the ocean²⁰, and support our aeolian transport thesis for the carbon particles.

We have made the implicit assumption that the extent of present day forests has persisted hundreds of thousands of years into the past (exclusive of glacial periods). Future work with the carbon contents of deep-sea sediments may reveal the validity of this concept. This work was supported by an EPA grant. D. M. S. is on leave from Hope College, and acknowledges an NSF fellowship.

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Man-made Objects on the Surface of the Central North Pacific Ocean

In August 1972, on the Scripps Institution of Oceanography's expedition C'BOG I in the Central North Pacific, there was a rare combination of clear warm weather and calm seas which tempted the scientific personnel to spend their leisure time on the bow of the ship. From this vantage point it was obvious that the sea surface is littered with a startling array of man-made objects, even 600 miles from the nearest major civilization (Hawaii) and outside the major shipping lanes.

A junk log was established and maintained (not continuously) for four days, during which time the ship travelled from 34° 29' N, 145° 36' W to 35° 00' N, 155° 00' W, and then south to 31° 00' N, 155° 00' W. Record was kept of the duration of watch, ship's speed and viewing conditions, and an effort was made to categorize each object, even though exact identification was often uncertain.

The results of this log are presented in Table 1. During 8.2 viewing hours during which time the ship travelled 156 km, and in approximately 12.5 km², a total of 53 man-made objects was recorded. Twelve of these were glass fishing floats, approximately 5 to 14 inches in diameter, which may claim some historic or aesthetic place on the sea surface. The remaining 41 objects were encountered with an average frequency of one every 12 minutes. At least two-thirds of these were plastic.

Succumbing to the temptation to extrapolate from our sample of six plastic bottles, we have calculated an average concentration of 0.5 bottle km⁻² (95% confidence interval, assuming a Poisson distribution: 0.2–1.0 bottle km⁻²) and a total of 35.4 million plastic bottles (14.2 × 10⁶–70.8 × 10⁶) currently adrift in the North Pacific Ocean (as well as 5.9 million red rubber sandals). A more conservative estimate may be derived from the observed ratio of plastic bottles to fishing floats, of which there are an estimated ten million afloat in the Pacific Ocean¹. Our ratio predicts five million plastic bottles.

Table 1 Tentative Identification of Man-made Objects adrift in the Central North Pacific Ocean

Plastic		Glass		Miscellaneous	
Bottles	6	Fishing floats	12	Rope	1
Fragments	22	Bottles	4	Old balloon	1
Total	28	Total	16	Finished wood	1
				Shoebrush	1
				Rubber sandal (red)	1
				Paper items	3
				Coffee can	1
				Total	9

On two of the plastic bottles, algal growth was evident. A third was covered with gooseneck barnacles. Floating plastic, like a glass fishing float, provides a long-lived substrate for transport of sessile animal species as well as algal and bacterial growth; whether the increased availability of such "micro-arks" might alter distributional patterns or attract local concentrations of associated pelagic organisms is an open question.

In the growing concern over global pollution, the accumulation of plastic products has received little attention. Widespread concentrations of plastic pellets have been reported in the Sargasso Sea². Although plastic objects may directly injure wildlife³, the inert nature of plastic means that it is unlikely to enter the food chain and threaten human welfare. As a pollutant, its effect is chiefly aesthetic, which is difficult to evaluate and easy to ignore. We find it alarming that "disposable" items now litter even the most remote surfaces of the oceans.

The production of plastics has evolved rapidly during the past twenty years—annual production of plastic bottles now exceeds 5 × 10⁹. The development of degradable plastics may bring some relief⁴, but unless we find adequate means of disposing

of our plastic products soon, we can anticipate that the "Wynkin, Blynkin and Nod" of our children will set sail into a plastic sea, accompanied by all the "no-deposit—no-return" products of our technology.

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Induced Nucleophilic Substitution in Benzo[a]pyrene

Cavalieri and Calvin have proposed^{1,2} that the carcinogenic action of benzo[a]pyrene (BaP) may arise from aryl hydroxylase induced binding to nucleophilic cellular components. Their theory proposes that attack by electrophilic oxygen, produced in the hydroxylase system, occurs at the 6 position of the hydrocarbon to give a carbonium ion, localized primarily at the 1 and 3 positions, which can undergo attack with nucleophilic cellular components. Alternatively, initial attack could occur at 1 or 3, followed by nucleophilic reaction at 6.

Some evidence for the theory has been obtained by using iodonium ion as a model for the hydroxylase system. Benzo[a]pyrene and iodine dipyrindine nitrate react to give either the 6-iodo or 6-pyridinium derivative or a mixture depending upon reaction conditions. Effects of solvent, concentrations and ratios of reactants were investigated and are summarized in Table 1. Equimolar quantities of the reagents react within 10 min in chloroform to give 6-iodo-benzo[a]pyrene in nearly quantitative yield. All other reactions listed required up to 24 h to reach completion. Formation of the pyridinium derivative requires a 2 : 1 molar ratio of iodonium reagent to BaP.

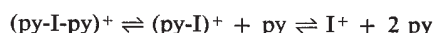
Table 1 Effect of Reaction Variables on Product Formation

Concentration of BaP	Molar ratios py-I-py [†] / BaP	Solvent	Yield, %	
			I-BaP	py-BaP
	1	CHCl ₃	99	Trace
	1	MeOH	95	
	1	DMF	95	
		Pyridine	No reaction	
1 mg ml. ⁻¹	32	1% py/CHCl ₃	50 [†]	50 [†]
0.5 mg ml. ⁻¹	64	1% py/CHCl ₃		95
5 mg ml. ⁻¹	30	5% py/CHCl ₃		95
5 mg ml. ⁻¹	30	5% py/CHCl ₃		50
1 mg ml. ⁻¹	2	CH ₃ CN		10

* Added pyridine.

† Approximate yields.

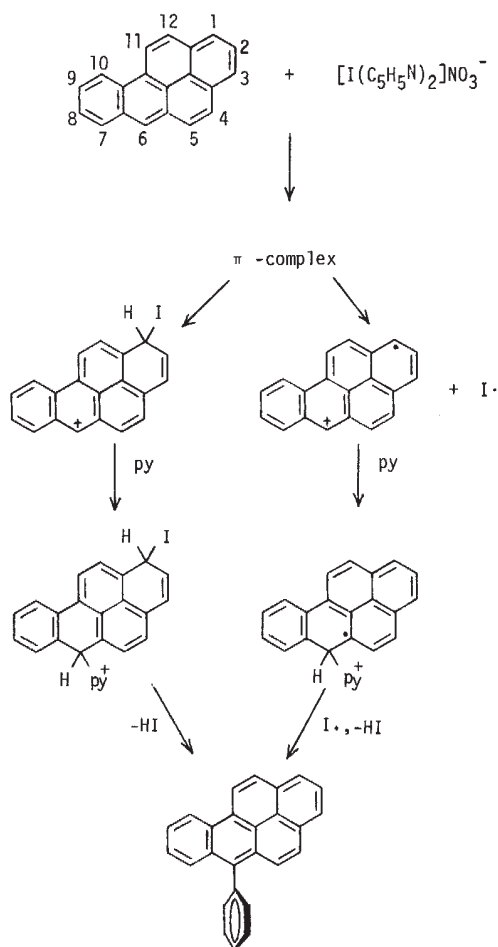
The formation of the 6-pyridinium derivative may be interpreted as arising *via* the proposed ionic mechanism with initial electrophilic attack occurring at position 1 or 3 rather than at position 6 as occurs in the formation of 6-iodobenzo[a]pyrene. The position of attack might change for steric reasons because different reagents could be involved as indicated by the following equilibria:



If formation of 6-iodobenzo[a]pyrene arises from attack by I^+ , the equilibrium in pyridine-chloroform will be displaced to the left and a bulkier reagent might attack at position 1 or 3, forming the 6-pyridinium derivative. Steric factors are important since acylation with succinic anhydride and aluminum chloride gives the product with substitution in the one position⁴. The excess pyridine present in the reaction mixture may also provide conditions where the addition of pyridine to the sigma complex formed by electrophilic attack at 1 or 3 is faster than the rate of elimination of a proton to give the 1- or 3-iodo derivative. The dihydro-disubstituted compound thus formed would then undergo elimination of HI to give the 6-pyridinium derivative.

The reaction can also be postulated to proceed *via* the radical cation of BaP. Although evidence has been found³ that the radical cation of BaP, produced by oxidation with iodine, reacts with pyridine to give the 6-pyridinium derivative, no radical was detected under the conditions of these reactions. The simple iodine reaction does not proceed under the conditions employed in this study.

Both the ionic and radical modes are shown in the following reaction scheme.



The structural assignments for the iodo and pyridinium derivatives are based on the ultraviolet and 220 MHz nuclear magnetic resonance spectra (Fig. 1). The ultraviolet spectra match reported spectra for 6-iodobenzo[a]pyrene⁵ and 6-pyridinium benzo[a]pyrene perchlorate³. The NMR assignments are based on comparison with the spectrum of the parent hydrocarbon^{6,7}, coupling constants, splitting patterns, and double resonance decoupling experiments. The NMR spectra of the pyridinium derivative establish the fact that the plane of the pyridine ring is perpendicular to the plane of the benzo[a]pyrene ring since protons 5 and 7 are shielded, relative to their

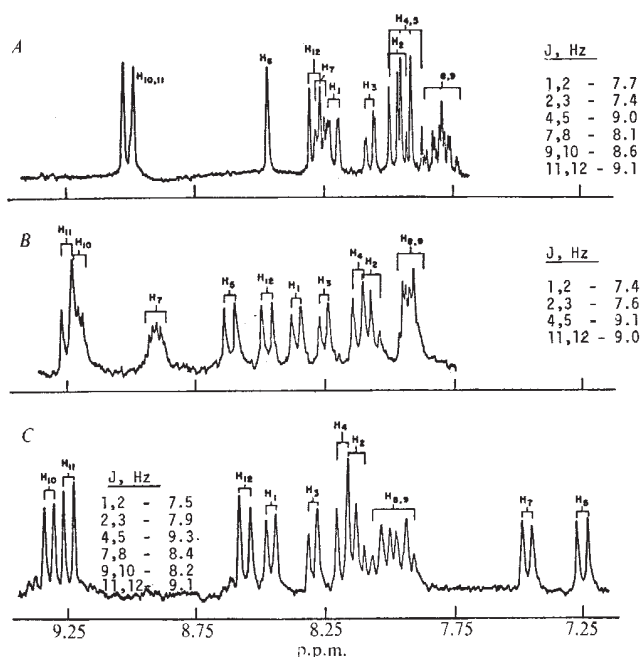


Fig. 1 220 MHz NMR spectra. A, Benzo[a]pyrene in $CDCl_3$; B, 6-iodobenzo[a]pyrene in tetrahydrofuran; C, the 6-pyridinium- d_5 derivative of benzo[a]pyrene in methanol.

positions in the parent compound, by the pyridine ring current. This is in contrast to the deshielding which all the protons, including 5 and 7, exhibit in the 6-iodo compound.

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BIOLOGICAL SCIENCES

Evidence for Naturally Occurring Murine Sarcoma Virus

THE origin of the murine sarcoma viruses (MuSV) found in tumours resulting from the injection of mice with leukaemogenic viruses (MuLV)¹⁻³ and from spontaneous tumours⁴ is very obscure. Viruses isolated from spontaneous tumours^{3,4} might have been induced through accidental horizontal transmission of Moloney sarcoma virus. The origin of isolates of Moloney sarcoma virus^{1,2} and Kirsten sarcoma virus⁵ is also unknown because the virus preparations used had been passaged through rats^{2,5} or mice of various strains for many years¹. Nor is it known whether sarcoma virus was present in the preparations of murine leukaemia virus

administered to the animals subsequently developing sarcomas. It has been suggested that Moloney MuSV is derived from Moloney MuLV⁶, but there may be an endogenous, latent sarcoma virus present in mice which could perhaps be activated by the administration of a leukaemogenic virus. We now report that a clone-purified MuLV, isolated from an established cell line in tissue culture and having *in vitro* no demonstrable content of MuSV, induced sarcomas in several strains of mice and MuSV could be readily isolated from these sarcomas. The virus was also present in the plasma of the tumour-bearing mice.

The virus used was obtained from a clone of JLS-V9 cells⁷ which, on routine passage, began to release spontaneously a murine leukaemia virus, positive in the XC assay⁸. Clone M4 was twice recloned following "turn-on" and the resulting chronically infected cell line served as the source of virus for this study. Cells were grown in Eagle's minimal essential medium with 10% heat-inactivated foetal calf-serum, penicillin and streptomycin. The tissue culture medium in which cells had grown was used as the stock of virus (JLS-V9MuLV) for these studies.

The cells used for the assay for transforming virus were 3T3 or TB cells. The latter were established from a mixed culture of thymus and bone marrow (J. K. B. and D. H., unpublished data) of CFW/D mice⁹ using the procedure of Wright *et al.*⁷. The assay for MuSV focus forming units (f.f.u.) was carried out by mixing 1×10^6 cells in suspension with an equal volume of the appropriate dilution of virus in the presence of 'DEAE-dextran'¹⁰. The suspension was shaken at 37° C for 40 min and 2×10^5 cells plated. Medium was replaced two days post plating and the number of foci determined on the third day. In some experiments a simultaneous assay for MuSV XC activity was carried out as described above except that following infection 500 cells were plated. XC cells were added three days post infection and syncytium positive clones were counted on day 4.

Table 1 Effect of Input Multiplicity of Infection (m.o.i.) of Added MuLV on Titre of a Constant Number of Focus Forming Units

M.o.i. of MuLV	Titre (f.f.u. ml. ⁻¹)	No. of determinations
30	1.5×10^5	2
15	2.0×10^5	2
8	2.7×10^5	3
4	6.8×10^5	6
2	12.9×10^5	6
1	14.5×10^5	6
0.5	9.0×10^5	3
0.25	5.5×10^5	3

Focus forming units (f.f.u.) assayed using TB cells.

The MuSV was a tissue culture harvest of cells (TB) infected with plasma from a mouse in which JLS-V9MuLV had produced a sarcoma.

Because the JLS-V9MuLV used in these studies was of high titre ($1-4 \times 10^8$) a very small content of MuSV might not be detectable by the focus assay. The measured titre of focus forming virus decreased when the multiplicity of MuLV surpassed an optimal level (Table 1). It was therefore necessary to dilute stock JLS-V9MuLV so that the input multiplicity of infection (m.o.i.) of MuLV was approximately two, and to infect enough cells to compensate for the dilution. The stock JLS-V9MuLV with 2×10^8 infectious units ml.⁻¹ (by XC assay) was diluted and mixed in suspension with 1.1×10^8 cells, all of which were plated at 2×10^5 cells per dish (60 mm diameter). The titre of MuLV in the medium three days post infection was 2×10^8 , showing that the cells had been infected, but no foci were seen in any dish. In many experiments where JLS-V9MuLV has been grown in a variety of cell cultures, including primary and secondary mouse embryo cells of CFW/D, NIH Swiss, Balb/c and CBA we have never seen foci of transformed cells. To check the sensitivity of this focus assay we assayed a preparation of Moloney MuLV virus that appeared to be free of sarcoma

Table 2 Incidence of Sarcomas Following Injection of JLS-V9MuLV into Various Strains of Mice

Strain	Group	Vol. injected (ml.)	No. of mice	No. of mice with tumours	Latent period (days)
CFW/D	I	0.05	55	50*	60-148
CFW/D	II	0.05	24	0	—
CFW/D	III	0.05	11	5†	70-90
CFW/D	IV	0.1	18	0	—
CFW/D	V	0.1	15	0	—
NIH Swiss ‡	VI	0.05	18	16	50-150
C3H/BI§	VI	0.05	10	5	40-110
C57Bl/6J	VI	0.05	11	5	50-190
CBA¶	VI	0.05	15	1	90

Group I, intraperitoneal injection into newborn mice.

Group II, injection directly into 7 day old thymus grafted under the kidney capsule of a normal, 6 week old recipient.

Group III, injection directly into 7 day old thymus grafted under the kidney capsule of recipients given 550 rad (whole body) before grafting.

Group IV, injection (intraperitoneal) into normal, 6 week old adults.

Group V, controls injected intraperitoneally with a compatible volume of tissue culture medium from noninfected JLS-V9 cells.

Group VI, intramuscular (thigh) injection into newborn mice.

* Includes 3 separate experiments using different tissue culture passage levels of JLS-V9MuLV.

† All tumours arose in muscle tissue underlying the kidney bearing the thymus graft or in the thigh (remote from site of injection).

‡ From NIH, Bethesda, Md.

§ From Dr H. S. Kaplan.

|| From Jackson Laboratory, Bar Harbor, Maine.

¶ From MRC, Mill Hill.

virus when tested in the usual way. We found it to contain 480 focus forming units per ml. MuSV and 2×10^8 MuLV per ml.

The stock of JLS-V9MuLV that contained no detectable MuSV was injected into mice less than one day old. The results are given in Table 2. The intraperitoneal injection of JLS-V9MuLV into newborn mice or adult mice exposed to X-irradiation induced multiple tumours many of which appeared simultaneously. Tumours arose in muscle (all four limbs), peritoneal wall, diaphragm, along the spinal column, in the dermis and on the head and face. Histologically, they resembled the rhabdomyosarcomas or atypical granulomas described for those induced by MuSV (Moloney)¹¹ and MuSV (Harvey)¹². In contrast to the latter tumours, the MuSV induced by JLS-V9MuLV produced no spleen enlargement in any of the tumour-bearing mice. All tumours grew progressively and killed their hosts. Transplantation to normal syngeneic adult mice resulted in initial tumour growth followed by complete regression, but in mice pretreated with 400 rad whole body irradiation there was progressive growth resulting in death of the animals. Tumours of this type have never been observed to occur spontaneously in CFW/D mice.

The undiluted virus stock resulted in a high tumour yield so the stock was diluted and injected intraperitoneally into mice less than one day old. The distribution of tumours and their biological behaviour, shown in Fig 1, was similar to that for the undiluted stock. If it is assumed that the tumour yield obtained with the 10^{-3} dilution of the virus was the result of a low level of MuSV present in the injected MuLV then the titre of such an MuSV would have been 1.6×10^5 f.f.u. per ml. (assuming that 1 f.f.u. would be sufficient to induce a tumour *in vivo*). The f.f.u. assay we used readily detected 480 f.f.u. ml.⁻¹ of MoMuLV (MuSV), and we therefore concluded that JLS-V9MuLV was free of transforming virus that can be detected *in vitro*.

To exclude the possibility that there was a small amount of pre-existing MuSV present in the JLS-V9MuLV which might have escaped detection *in vitro* but was selected for *in vivo*, the JLS-V9MuLV was clone purified. Cells of an established line (TB) were infected in suspension with

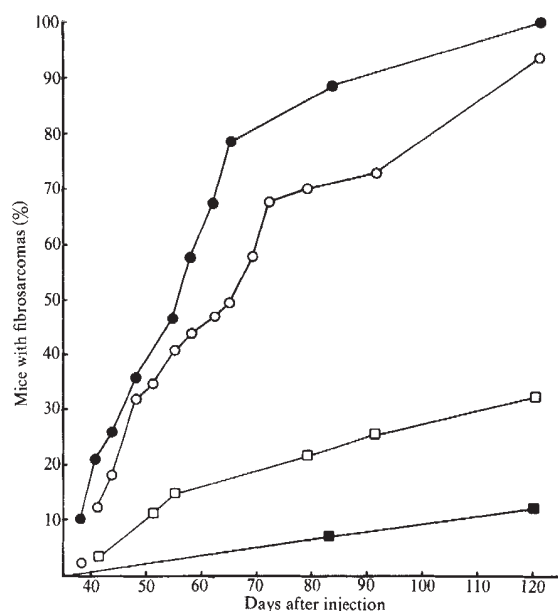


Fig. 1 Effect of dilution of JLS-V9MuLV on the incidence of fibrosarcomas in CFW/D mice. Newborn mice were injected with the following dilutions of tissue culture supernatant from chronically infected JLS-V9MuLV infected cells: ●, 0.05 ml. undiluted; ○, 0.1 ml. 10^{-1} dilution; □, 0.1 ml. 10^{-2} dilution; ■, 0.1 ml. 10^{-3} dilution. There were 24–34 mice per group.

a limiting dilution of JLS-V9MuLV and plated at 500 cells per plate. Three days post plating the medium was removed and replaced with medium containing 5×10^5 XC cells⁸. When these cells had attached (six hours after plating) the medium was replaced with medium containing 0.7% agar. The plates were incubated for a further 24 hours and then the agar immediately above an infected (XC positive) cell clone was picked and added to 1 ml. containing 1×10^5 normal TB cells in complete medium containing polybrene¹³. Following absorption the cells were plated, grown for three days when the medium was changed, and after a further 24 h the medium from a number of dishes, each infected with a different clone of JLS-V9MuLV, was collected and assayed for MuLV using the XC assay¹⁴. Five clones of JLS-V9MuLV were obtained having titres between 1.2 – 1.8×10^6 , and each was tested by injecting approximately twenty newborn CFW/D mice with 0.1 ml. of cell-free tissue culture supernatant. All JLS-V9MuLV clones were positive for rhabdomyosarcoma induction by 45 days post infection. This shows that fibrosarcomas can be induced in mice by an MuLV which does not contain any MuSV.

Plasma from tumour-bearing mice and extracts of tumours¹⁵ induced by JLS-V9MuLV were active *in vivo* for sarcoma induction in mice (NIH Swiss, Balb/c, CFW/D) and *in vitro* for both MuSV and MuLV activity. Assayed by the method of Hartley and Rowe¹⁶ the plasma contained approximately 3×10^3 f.f.u. ml.⁻¹. Tumour extracts contained an average of 1×10^7 MuLV g.⁻¹ of tumour by the XC assay and 1×10^5 f.f.u. g.⁻¹ of tumour when assayed by the suspension-infection method described here. Such virus preparations were inactive when injected into newborn W/Fu rats (Microbiological Associates).

Only CBA mice proved refractory of all mouse strains tested, but this resistance was not found when CBA mice were injected with MuSV obtained from a JLS-V9MuLV induced tumour. Under these conditions CBA mice were as sensitive as CFW/D and NIH Swiss mice.

The results of a titration *in vivo* in CFW/D mice of plasma derived from mice bearing JLS-V9MuLV induced tumours are given in Table 3. Two different preparations of plasma were used in this experiment, but the data were

pooled as both gave virtually identical results. The highest concentrations of virus resulted in rapid induction of tumours, whereas more dilute concentrations resulted in a high incidence of tumours with a long latent period. It appeared that there were two periods of time in which tumours arose in response to the injection of plasma, one with a short mean latent period with the high concentration of plasma and the other, separated from the first by a gap in time, with a mean latent period corresponding exactly with that found for tumours arising in mice injected with tissue culture preparations of JLS-V9MuLV.

Table 3 Incidence and Average Latent Period of Neonatal Sarcomas (CFW/D Mice) induced by Plasma from Mice Bearing Tumours Induced with JLS-V9MuLV

Plasma dose	Volume (ml.)	Mice*	Tumours*	Average latent period (days)†	% Tumours
Undiluted	0.05	13	13	21*	100
10^{-1}	0.1	20	20	20	100
10^{-2}	0.1	32	24	26	
			8	53 < 52 ‡	100
				58	
10^{-3}	0.1	28	4	21	
			21	72 < 48	90
				150	

* One mouse developing a tumour on day 94 excluded from group.

† Time to first appearance of tumour.

‡ Times at which earliest and latest tumours appeared.

The results of these experiments suggest that, first, a focus forming virus is responsible for the early arising tumours and, second, a virus which can activate a sarcoma inducing activity is responsible for the late appearing tumours. Experiments are in progress to correlate the levels of these two viral activities with early and late appearing tumours, and preliminary data suggest there is a correlation.

To explain the experimental results obtained we suggest that JLS-V9MuLV could function by: (1) containing the necessary genetic information for MuSV which can be expressed *in vivo* but not *in vitro*, (2) JLS-V9MuLV can "activate" a latent endogenous MuSV, (3) JLS-V9MuLV might recombine genetically with oncogenic information¹⁷ *in vivo*. We are now testing these models. Studies of the relationships between MuLV and MuSV should be aided by the reproducible recovery of MuSV directly from animals, thus avoiding passage through animals and/or tissue culture.

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Puromycin Stimulation of Rat Liver Ornithine Decarboxylase Activity

It is well known that puromycin inhibits protein synthesis in mammalian systems¹, but other metabolic effects have been reported²⁻⁵. Our own work on the purification of rat liver ornithine decarboxylase (ODC)⁶, the apparent rate-limiting enzyme in polyamine synthesis, led us to a study of hormonal factors which alter the activity of this enzyme. We found that dibutyl-*l*-cyclic adenosine 3',5'-monophosphate (dibutyl-*l*-cyclic AMP) stimulated hepatic ODC activity in normal rats^{6a}. When actinomycin D, which had no independent effect on the basal level of the enzyme, was given with dibutyl-*l*-cyclic AMP, ODC activity was inhibited. However, when the animals were dosed with either puromycin alone or puromycin and dibutyl-*l*-cyclic AMP at levels of puromycin which inhibited protein synthesis, the antibiotic alone stimulated ODC activity and potentiated the activity due to dibutyl-*l*-cyclic AMP.

The effect of a single intraperitoneal administration of puromycin to normal rats indicates a clear stimulation of hepatic ODC activity, reaching a peak of 71.7 units (U) after 3.5 h, a more than fourteen-fold increase over zero time controls (Fig. 1A). The activity then fell off to 15.2 U, or slightly more than 20% of the 3.5 h activity. Fig. 1A shows that saline had no effect of its own; these latter values varied, as did the non-injected control values, between 2.2 and 11.5 U during 5 h. This figure also shows that a single intraperitoneal administration of dibutyl-*l*-cyclic AMP to normal rats stimulated hepatic ODC activity. Peak activity occurred 2-3 h after dosing, and this was an earlier maximum response than that seen after puromycin administration. Two hours after dosing with dibutyl-*l*-cyclic AMP, the ODC activity was 40.3 U, a more than eight-fold increase over the zero time value of 4.9 U. The dibutyl-*l*-cyclic AMP-stimulated ODC activity increased slightly to 44.6 U by 3 h and then fell to values ranging from 12.2 to 14.5 U between 3.5 and 5 h after drug administration.

The synergistic effect of dibutyl-*l*-cyclic AMP and puromycin is seen when these two compounds are administered concurrently. Whereas at 2 h a preliminary decrease in ODC activity was seen (10.9 U, a 73% decrease compared with animals given dibutyl-*l*-cyclic AMP alone), by 3 h the ODC activity was 167 U. This greater than thirty-five-fold stimulation over the zero time value was more than additive, since the combined activities of the dibutyl-*l*-cyclic AMP and puromycin alone were 79.3 U. The peak puromycin dibutyl-*l*-cyclic AMP-stimulated activity (175 U at 3.5 h) occurred when the dibutyl-*l*-cyclic AMP-stimulated activity had returned to 13.2 U. The puromycin/dibutyl-*l*-cyclic AMP-stimulated activity then decreased to 48.9 U by 5 h, a value equivalent to the maximum activity obtained with dibutyl-*l*-cyclic AMP alone (44.6 U).

We tried to correlate the time sequence of inhibition of protein synthesis by puromycin with the stimulation of ODC activity. Puromycin or puromycin plus dibutyl-*l*-cyclic AMP depressed protein synthesis by more than 60% after

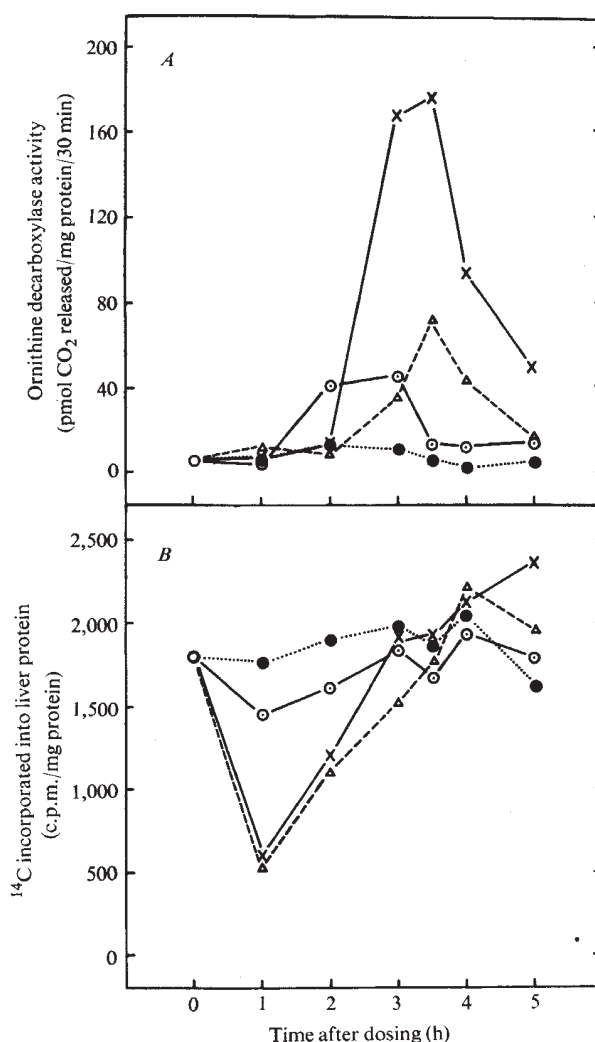


Fig. 1 Effect of puromycin and dibutyl-*l*-cyclic AMP on (A) rat liver ornithine decarboxylase activity and (B) radioactivity from ¹⁴C-leucine injection incorporated into total liver protein. Male, Sprague-Dawley rats (140-160 g) were used, and chemicals were obtained from commercial sources. The rats were fasted overnight, with a minimum of 15 h of food deprivation before death. Rats were injected intraperitoneally at zero hours with either puromycin (Δ), 12 mg in 0.2 ml. isotonic NaCl; neutralized/100 g body weight, dibutyl-*l*-cyclic AMP (○), 2 mg in 0.2 ml. isotonic NaCl/100 g body weight, puromycin + dibutyl-*l*-cyclic AMP (×), or isotonic NaCl (●), 0.2 ml./100 g body weight. A, The preparation of the 100,000g supernatant fraction and the assay of ODC activity by trapping ¹⁴CO₂ released from (1-¹⁴C)-DL-ornithine have been described (refs. 6 and 6a). One unit of enzyme activity is expressed as pmol ¹⁴CO₂ released per mg protein per 30 min. Protein was measured by the biuret method⁷, using bovine albumin as a standard. The results presented for each point represent the mean of three to eight animals; each individual assay was done in triplicate. The standard errors varied from 15 to 20% in all cases, and the statistical analysis of the data was determined using the *t* test. B, All animals received an intraperitoneal injection of 15 μCi/100 g body weight (1-¹⁴C)-L-leucine (28.7 mCi/mmol) 20 min before killing. It was ascertained experimentally that the ¹⁴C-leucine administered to the rats did not interfere with the assay of ODC activity. To determine the amount of ¹⁴C incorporated into liver protein, aliquots of the whole homogenate were precipitated with 5% trichloroacetic acid (TCA), heated at 80-90° C for 15 min, cooled and centrifuged. The samples were washed twice in 5% TCA, extracted with hot ethanol (70° C for 15 min), centrifuged, resuspended in TCA and centrifuged again. The pellets were dissolved in 0.1 N NaOH and aliquots were counted for radioactivity. Protein was measured by the method of Lowry *et al.*⁸, using bovine albumin as a standard.

1 h (Fig. 1B), at a time when no differences in ODC activity were discernible (Fig. 1A). However, Fig. 1B shows that the ODC activity increased and reached a maximum when

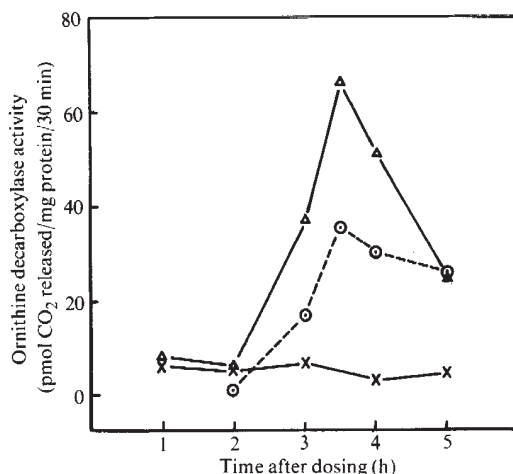


Fig. 2 Effect of puromycin and actinomycin D on rat liver ornithine decarboxylase activity. Conditions were as in Fig. 1. Rats were injected intraperitoneally with either puromycin (Δ), 12 mg in 0.2 ml. isotonic NaCl, neutralized/100 g body weight, actinomycin D ($\times$), 80 μ g/100 g body weight (the drug was dissolved in a minimal volume of 50% ethanol and brought to volume with 0.9% NaCl), or puromycin+actinomycin D ($\circ$). As in Fig. 1A, one unit of enzyme activity is expressed as pmol $^{14}\text{CO}_2$ released per mg protein per 30 min. The results presented for each point represent the mean of three to eight animals, and the standard errors ranged from 5 to 25% in all cases. The dose of actinomycin D was selected as the optimal dose which prevents any increase in incorporation of ^{14}C -orotic acid into hepatic nuclear and cytoplasmic RNA¹³.

the puromycin inhibition of protein synthesis was terminated (3 h); dibutyryl-cyclic AMP slightly depressed protein synthesis, but this was not statistically different from controls.

The effect of actinomycin D on the puromycin-stimulated ODC activity was to reduce the peak at 3.5 h by 47% (Fig. 2). However, the increase in ODC activity was still appreciable at this time (35.4 U). The decline of enzyme activity from livers of animals treated with these drugs was less rapid than that seen with the enzyme from animals treated with puromycin alone, an activity of 75% (25.4 U) of peak values being reached by 5 h. Fig. 2 also shows that actinomycin D alone had no stimulatory effect on hepatic ODC activity.

We may consider some explanations for the puromycin effect. If the assumption is made that there exists a protein inhibitor of ODC which is more sensitive than ODC to the actions of puromycin, then after the administration of the drug, at a time of maximal depression of protein synthesis, the production of both the inhibitor protein and the ODC would cease. However, as puromycin levels decrease, protein synthesis would resume, but the inhibition of ODC would be relieved first, thus causing a rise in ODC activity. Alternatively, it may be possible that because puromycin causes an extensive inhibition of protein synthesis, this produces an accumulation of the ODC messenger RNA, subsequently resulting in a "rebound" phenomenon of greatly enhanced ODC activity when the drug effect was terminated. Both of these hypotheses are consistent with the kinetics of inhibition presented in Fig. 1 and are amenable to experimental verification.

Such facile explanations, however, should be tempered by the complexities inherent in the metabolism of eukaryotic cells, and other explanations for the puromycin effect are possible. For example, partial hepatectomy results in an increased amino-acid content of hepatic cells⁹⁻¹¹; at the same time, ODC activity increases¹²⁻¹⁸. In addition, cyclic AMP increases the hepatic content of free amino-acids¹⁹, and administration of dibutyryl-cyclic AMP^{6a} or a mixture of amino-acids¹³ increases ODC activity. It is thus conceivable that the inhibition of protein synthesis by puromycin also increases hepatic amino-acid pools which then

act as a causal stimulus for increased ODC activity.

Other possibilities may be considered. (a) Puromycin may increase endogenous levels of cyclic AMP with consequent increases in ODC activity; such an explanation has been proposed for changes in the activities of glycolytic enzymes by puromycin^{3,20}. However, the same dose of actinomycin D which completely inhibits the dibutyryl-cyclic AMP stimulation of ODC activity^{6a} only partially inhibits the puromycin effect. (b) The drug may release nascent polysomal ODC molecules. It is known that both cyclic AMP and puromycin can release nascent protein and active enzyme from polysomes *in vitro*^{21,22}, but these effects were not found *in vivo*²³. Furthermore, this explanation might require the peak in ODC activity to occur at the time of the maximum effect of puromycin on protein synthesis; this, as has been shown, is not the case. (c) It has been shown that steroids increase ODC activity (refs. 6a, 24 and 25). Thus it is possible that puromycin administration stresses the animals severely enough to cause the release of adrenal cortical hormones. All these considerations are suitable for experimental investigation.

Finally, the enhancement of ODC activity in normal rats should not be confused with the "paradoxical" effect of puromycin in augmenting the already high enzymatic activities of foetal tissues or of hydrocortisone-stimulated preparations^{23,26-29}. Whereas a low dose of actinomycin D inhibits the puromycin-stimulated ODC activity (Fig. 2), the drug has been shown to "super-induce" tyrosine aminotransferase in tumour cells^{30,31}.

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Cholinesterase Inhibitors: Structure of Eserine

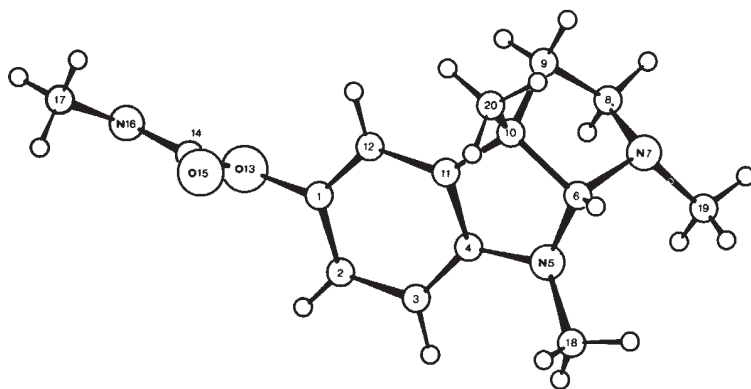
ESERINE (physostigmine) was first isolated from the Calabar bean in the latter half of the last century¹, but it was not until much later that its activity on the heart was demonstrated to be due to inhibition of acetylcholinesterase^{2,3}. It is one of the few compounds that are equally active as inhibitors of both true and pseudo-cholinesterase and has been used by many workers as a reference standard in the evaluation of new cholinesterase inhibitors. The chemical structure of this alkaloid was elucidated by Stedman⁴ and the absolute configuration has relatively recently been confirmed by use of the nuclear Overhauser effect (NOE) in NMR spectroscopy⁵. As part of our study of the geometry of molecules affecting cholinergic nervous transmission, we have determined the crystal structure.

ment with the results of the NOE study⁵. In solution there is no inversion of configuration by C18 and the lone pair on N5 (ref. 5), but the second pyrrolidine ring may be expected to be conformationally rather flexible because of inversion through N7. In the crystal, the lone pair on N7 is also *cis* to the hydrogen atom on C6. The carbamate group is planar, with the hydrogen on N16 *trans* to the keto oxygen, and will remain so in solution because of the partial double bond C14–N16. In the crystal, the torsion angle C12–C1–O13–C14 is observed to be -72° , but an examination of CPK space-filling atomic models indicates that this angle may range -30° to -150° and $+30^\circ$ to $+150^\circ$: the value of 31.8 observed by us in the crystal structure of neostigmine bromide⁷ is clearly a lower bound and no sign of a similar interaction between the *ortho* aromatic proton and the keto oxygen exists in the present structure.

Chothia and Pauling⁸ have postulated a particular conformation of acetylcholine as being the conformation relevant to interaction with the esterase, and Pauling and Petcher⁷ have pointed out the similarity between this postulated conformation and the observed solid-state conformation of neostigmine. It is difficult to correlate the conformation of eserine with these two because of the *para* relationship of N5 and the carbamate group in eserine. The observed conformations of eserine and neostigmine are, however, similar in some respects. The N5–C14 and N5–O15 distances are 638 and 620 pm respectively, compared with 605 and 647 pm in neostigmine. AChE appears to be relatively insensitive to molecular shape as far as reversible inhibition is concerned, provided that three necessary groups are present, these being a carbamate group bonded to an aromatic ring which must carry an alkyl substituted nitrogen atom in the *meta* or *para* position.

We thank Dr Hanspeter Weber for making available to us

Fig. 1 Perspective drawing of eserine, projected on the plane of N5–N7–C9–C11. The absolute configuration corresponds to that of the natural alkaloid.



Crystals of eserine (BDH Ltd), as clear tabular plates, are orthorhombic, space group $P2_12_12_1$, with $a=1458$ (1), $b=1435$ (1), $c=727.1$ (6) pm. Three-dimensional intensity data were measured on a computer-controlled⁶ four-circle diffractometer using graphite monochromatized MoK_α radiation. 2,658 measurements for $2\theta \leq 60^\circ$ yielded 2,556 symmetry-independent observations, of which 1,520 were significantly above background ($I \geq 3\sigma(I)$). The structure was solved by application of multi-solution direct methods and refined by block-diagonal least squares using anisotropic temperature factors for C, N and O, and isotropic vibrations for hydrogen. The present values of R are 0.060 over the 1,520 significant reflexions and 0.097 over all 2,531 data.

The conformation of the molecule is shown in Fig. 1, in the absolute configuration corresponding to that of the natural alkaloid. The two pyrrolidine rings are *cis*-fused, and that adjacent to the aromatic ring is practically flat, while the other is in the half-chair (C_2) conformation with the two-fold axis passing through C8 and the centre of the C6–C10 bond. Both ring nitrogen atoms are tetrahedral, but N5 is rather flattened and has more sp^2 character, judging from the bond angles. The C18 methyl group is *cis* to the hydrogen on C6, in agree-

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Circulating Sensitized Lymphocytes in Systemic Lupus Erythematosus

SYSTEMIC lupus erythematosus (SLE) is a classical autoimmune disease in man associated with the presence of autoantibodies to DNA and other self-antigens¹. It is not clear whether specifically sensitized lymphocytes active as effector cells of cell-mediated immunity (CMI) to DNA are also present. Inhibition of leucocyte migration^{2,3}, lymphocyte transformation in the presence of DNA^{4,5} and destructive effects of lymphocytes from SLE against human cells *in vitro*⁶ have been reported. It has also been claimed that lymphocytes in SLE are unresponsive to mitogens⁷ and that an inhibitor of leucocyte migration reflects depressed CMI⁸.

Here we report the direct cytotoxic activity of peripheral blood lymphocytes from SLE against target cells coated with DNA. We consider that this complement independent cytotoxicity probably reflects the activity of T lymphocytes in man, by analogy with experiments in mice^{9,10}.

We examined four women with a typical clinical picture of SLE. Three were in an active stage with LE cells in the blood and antinuclear antibody, while the fourth (M. M.) was in remission and immunologically inactive without anti-DNA antibody (see Table 1). Patient F. L. showed splenomegaly with thrombocytopenic purpura, the other three cases had connective tissue disturbances.

The results and experimental details are shown in Table 1. Lymphocytes were incubated with control target cells without antigen, and with target cells coated with purified tuberculin, microsomal fractions of human thyrotoxic glands, human thyroglobulin, and DNA. Cytotoxic activity of the lymphocytes was demonstrated in all patients in an active stage of SLE: against DNA antigen in patients F. L. and Ch. E., and against TG antigen in patients F. L. and P. Y. One patient,

Ch. E., showed a very high specific cytotoxic activity of the peripheral lymphocytes directed only against DNA coated cells. Tests for thyroid autoantibodies were negative in patients F. L. and P. Y., and antinuclear antibodies were detectable in the absence of cytotoxic activity to DNA coated target cells in P. Y. In the one case of SLE in remission no cytotoxic activity of lymphocytes was detected, neither were antibody or LE cells present. The effect of addition of rabbit antiserum against human lymphocytes to the incubation mixtures of lymphocytes, from patient P. Y., with DNA coated target cells is shown in Fig. 1. The cytotoxic activity of the lymphocytes was strongly inhibited in comparison with control normal rabbit serum.

Autoantibodies are important in the pathogenesis of the disorders of SLE¹. Lymphocytes sensitized to self antigen may also occur and affect the disease process. It has been claimed that the skin lesions of SLE resemble the changes seen in delayed-type hypersensitivity¹¹. Direct cytotoxicity of lymphocytes on allogeneic cells in the absence of complement has been shown to be mediated by T cells in mice^{9,11}. Similar cytotoxic activity of human lymphocytes in the absence of complement has been considered to be dependent on T cells¹². Direct proof of T cell involvement is not possible in the absence of specific antiserum to human T cells, but the inhibition of cytotoxicity by ATS in these experiments also suggests T cell participation. The presence of sensitized T cells in SLE and other autoimmune diseases raises two important possibilities. First, such lymphocytes could be directly cytotoxic *in vivo* to any cells carrying the appropriate antigen on their surface. In this way sensitized lymphocytes might participate in lesions. Second, these lymphocytes could function as "helper" cells¹³, cooperating with B cells, and might initiate antibody production.

There is evidence that in SLE the appearance of antibodies to DNA follows chronic bacterial¹⁴ or viral¹⁵ infections. It

Table 1 Comparative Results in Systemic Lupus Erythematosus

Patient	Sex	Age	Antinuclear antibodies*	Thyroid antibodies		LE cell phenomena	Lymphocytes§ incubated with mastocytoma target cells¶				
				TRC†	CFT‡		a, Non-coated	b, Coated PPD	c, Coated MC	d, Coated DNA	e, Coated TG
F. L.	F	51	Positive	Negative	Negative	Positive	4.04	6.25	7.16	14.64	37.57
Ch. E.	F	46	Positive	**	**	Positive	0.92	7.72	2.79	40.99	2.17
M. M.	F	51	Negative	**	**	Negative	2.24	6.30	1.46	0.00	0.00
P. Y.	F	23	Positive	1/25	Negative	Positive	4.09	8.29	5.86	6.24	21.98
Controls							Mastocytoma target cells				
With normal lymphocytes (n=number of donors)						n=	12	11	14	8	12
						$\bar{x}$ =	2.55	5.34	3.38	2.30	3.75
						s.e.m.=	0.76	0.92	0.80	0.90	0.99

* Detected using immunofluorescence technique.

† Haemagglutinin antibody titre determined by thyroglobulin haemagglutinating test (TRC).

‡ Complement fixing antibody titre determined by thyroid complement fixing antigen (CFT).

§ Prepared from defibrinated blood containing 100 mg per 10 ml. carbonyl iron powder. Separation by sedimentation, following 1 h incubation at 37° C, in 3% dextran and Eagle's medium containing 10% inactivated calf foetal serum (CFS). Lymphocytes were washed three times, iron particles and phagocytic cells removed and erythrocytes lysed when necessary by 0.83% ammonium chloride. Lymphocytes were 95 ± 2% pure.

|| Mouse P-815 mastocytoma cells (DBA/2 strain) labelled with sodium chromate 51 (1 mCi ml.⁻¹; specific activity 200–700 mCi mg⁻¹ chromium). Labelled cells (2 × 10⁶) suspended in 0.5 ml. Tris buffered saline, pH 7.2 and incubated for 1 h with 0.5 ml. of 2 mg ml.⁻¹ ECDI (N-ethyl-N'-(3-dimethylamino-propyl)-carbodiimide-HCl). Excess antigen removed by washing six times with Eagle's medium.

¶ Cells coated with 2 ml. of: 2.5 mg ml.⁻¹ herring sperm DNA; 2.5 mg ml.⁻¹ human thyroglobulin (TG); 350 µg ml.⁻¹ microsomal fractions of human thyrotoxic glands (MC); 500 µg ml.⁻¹ purified tuberculin (PPD). Cell viability was tested with trypan blue.

¶ One ml. of 2.5 × 10⁶ cells ml.⁻¹ lymphocytes mixed with 0.1 ml. viable target cells 5 × 10⁴ cells ml.⁻¹. After mixing with 5% CO₂ in air and incubation in sterile sealed tubes at 37° C for 15 h, they were centrifuged for 5 min at 1,500 r.p.m. Assay of supernatant for ⁵¹Cr used a deep-well scintillation counter. Results expressed as "cytotoxic index":

$$\frac{\text{Experimental } ^{51}\text{Cr release} - \text{spontaneous } ^{51}\text{Cr release}}{\text{Maximal } ^{51}\text{Cr release} - \text{spontaneous } ^{51}\text{Cr release}} \times 100$$

Maximum release of ⁵¹Cr from labelled target cells incubated in distilled water was 82%, spontaneous release in Eagle's medium with CFS was 19 ± 3%.

** Not measured.

is also possible that autocytoxicity to lymphocytes¹⁶ may result in enucleation of lymphocytes and the expression of self-DNA. Such mechanisms may explain the emergence of sensitized lymphocytes as a response to either non-self DNA antigens. The presence of lymphocytes sensitized to self antigen in SLE has a counterpart in Hashimoto's disease, where lymphocytes sensitized to thyroglobulin have also been demonstrated¹².

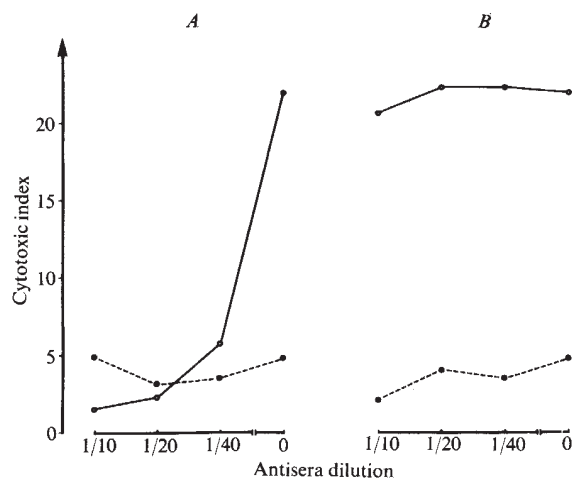


Fig. 1 Inhibitory action of rabbit antiserum against human thymocytes. Rabbit antiserum against human lymphocytes (A) and control rabbit serum (B) were inactivated for 30 min at 56°C and absorbed with human AB, Rh⁺ red blood cells. ○—○, Lymphocytes from SLE (P. Y.); ●—●, normal lymphocytes.

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Chronoperiodicity in the Response to the Intra-amniotic Injection of Prostaglandin F_{2α} in the Human

CIRCADIAN rhythms in susceptibility to drugs are well documented, both in laboratory animals and man, and as a consequence the concepts of circadian chronopharmacology, chronotoxicology and chronotherapy have developed¹. Although there is a most marked circadian rhythm in the incidence of spontaneous delivery in women², there appear to have been no studies of the chronopharmacology of drugs, such as oxytocin and the prostaglandins, used in the induction of labour or abortion.

In a study of factors influencing the induction-abortion interval following the intra-amniotic injection of prostaglandin F_{2α} (PGF_{2α}), it became obvious that there was an association between the duration of this interval and the time of injection. This communication reports the results from a study of sixty nulliparous and thirty parous women, between the 12th and 20th weeks of gestation, concerning the relationship between the time of injection of PGF_{2α} and the subsequent interval to abortion.

This study was carried out during the period March–July 1972 using a standardized procedure in which PGF_{2α} was injected transabdominally into the amniotic sac in a dose of 30 mg, followed, if necessary, by doses of 15 mg at 24 h and 42 h. All the patients were admitted to hospital at least 4 h before treatment and were allowed to eat at the normal meal times of 7 a.m., midday and 5 p.m. The PGF_{2α} treatment was initiated at various times within the period 8 a.m. to 10 p.m.

No other drugs except pethidine (for analgesia) and metoclopramide or 'Debendox' ('Debendox' [Wm. S. Merrell]: dicyclomine hydrochloride 10 mg, doxylamine succinate 10 mg, pyridoxine hydrochloride 10 mg, for nausea and vomiting) were administered between the time of admission and subsequent abortion.

Table 1 Effect of Time of Intra-amniotic Injection of PGF_{2α} upon Subsequent Induction-Abortion Interval

Parity of patient	Mean induction-abortion interval (hours ± s.e.)		Significance of difference P <
	6 p.m. injection	Injection at all other times within 8 a.m.–10 p.m. period	
Nulliparous	10.5 ± 1.1 (8)	28.0 ± 1.6 (52)	0.001
Parous	10.3 ± 1.8 (6)	22.1 ± 1.8 (24)	0.005
Total patients	10.4 ± 1.0 (14)	26.2 ± 1.3 (76)	0.001

The number of patients is shown in parentheses.

The induction-abortion interval was found to be significantly influenced by both parity of the patient and the time of administration of PGF_{2α}. The mean induction-abortion interval (± s.e.) for parous women, 19.7 ± 1.7 h, was less ($P < 0.05$) than that for nulliparous women, 25.6 ± 1.6 h. The induction-abortion interval was shortest when the initial injection of PGF_{2α} was administered at 6 p.m. (Table 1) and showed a distinct chronoperiodicity in nulliparous women (Fig. 1). There was no apparent relationship between the duration of the induction-abortion interval and stage of gestation, medication with drugs, time of hospitalization or time of eating.

In the nulliparous group, the mean induction-abortion interval was significantly less following PGF_{2α} administration at 5 p.m.–7 p.m. than at any other time (compare 8 a.m.–10 a.m., 8 p.m.–10 p.m. and all times except 5 p.m.–7 p.m., $P < 0.001$; cf. 11 a.m.–1 p.m., $P < 0.005$; cf. 2 p.m.–4 p.m., $P < 0.01$) and was significantly less ($P < 0.001$) at 6 p.m. than at either 5 p.m. or 7 p.m. (Table 2).

These findings have immediate clinical implications because

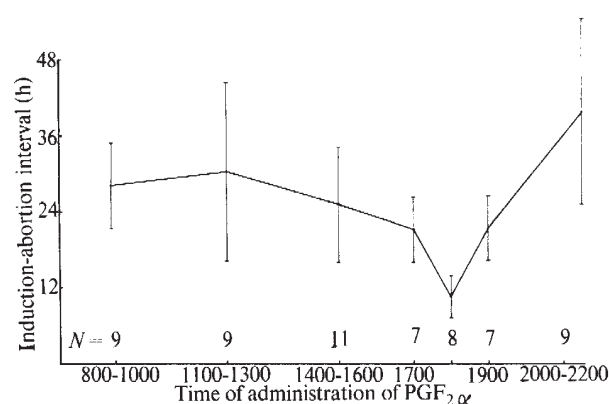


Fig. 1 Relation of time of intra-amniotic injection of $\text{PGF}_{2\alpha}$ to induction-abortion interval in nulliparous women (mean $\pm$ s.e.).

the induction-abortion interval influences the total dose of $\text{PGF}_{2\alpha}$ administered, the duration of hospitalization and the duration of exposure to side-effects of $\text{PGF}_{2\alpha}$ (which can be quite unpleasant). Further, a protracted induction-abortion interval produces severe anxiety in most patients. In terms of the total dose of $\text{PGF}_{2\alpha}$ required to terminate the pregnancy, there is a highly significant difference ($P < 0.002$) between the group treated at 5-7 p.m. and the group treated at other times: of those treated at 5-7 p.m., 74% required only a single dose of 30 mg whereas 63% of those treated at other times required a total dose of 45 mg or more. None of the patients treated at 6 p.m. required more than the initial dose of 30 mg of $\text{PGF}_{2\alpha}$. Although a not inconsiderable percentage (43%) of women injected at 6 p.m. aborted within 8 h, no women injected at any other time aborted in less than 9 h.

Table 2 Chronoperiodicity in Response to the Intra-amniotic Injection of $\text{PGF}_{2\alpha}$ in Nulliparous Women

Time of injection	Number of patients	Induction-abortion mean $\pm$ s.e.	Interval (h) range
8 a.m.-10 a.m.	9	28.0 $\pm$ 2.3	19.25-45.0
11 a.m.-1 p.m.	9	30.2 $\pm$ 4.7	9.1-51.8
2 p.m.-4 p.m.	11	25.1 $\pm$ 2.7	13.25-43.74
5 p.m.-7 p.m.	22	17.3 $\pm$ 1.4	6.0-28.5
8 p.m.-10 p.m.	9	39.7 $\pm$ 4.9	12.0-61.0
All times except 5 p.m.-7 p.m.	38	30.5 $\pm$ 2.1	9.1-61.0

Because the duration of the induction-abortion interval is an individually unique rather than a recurrent parameter, it might be expected to be difficult to demonstrate a circadian rhythm; nevertheless, the present observations establish unequivocally that the duration of this interval is a chronoperiodic phenomenon. In view of the fact that intra-amniotically injected $\text{PGF}_{2\alpha}$ appears to be slowly transferred from the amniotic compartment³, it would seem remarkable that a difference of 1 h in either direction from 6 p.m. can double, or increase by more than 10 h, the mean induction-abortion interval.

The observed periodicity in response to the intra-amniotic injection of $\text{PGF}_{2\alpha}$ must, undoubtedly, be related to endocrine and/or other rhythmic metabolic changes. Although it would be premature to speculate concerning the factors involved in the chronoperiodicity of this response, the similarity of the pattern of response to the intra-amniotic injection of $\text{PGF}_{2\alpha}$ to that of the circadian rhythm in salicylate excretion time⁴ is too obvious to avoid comment; the salicylates have been shown⁵ to inhibit prostaglandin synthesis and release.

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Papilloma Induction in Different Aged Skin Grafts to Young Recipients

THE incidence of malignancy in lymphoid tissue increases with age in BALB/c mice¹. This could reflect either a deterioration of the immune surveillance mechanisms of the animals or there may be an increasing rate of malignant transformation of lymphoid cells with increasing age. Some evidence for the latter suggestion has been obtained by transferring lymphoid cells from old and young non-malignant syngeneic donors to young BALB/c recipients. Reticular tumours developed with an incidence that was three times higher in recipients of old cells than in mice which received young cells¹. Interpretation of my results, however, was limited by an inability to determine whether the tumours were derived from donor cells or host cells. In an attempt to overcome this problem I have investigated here tumour development on skin grafts transferred from old and young syngeneic donors to young recipients. Inbred BALB/c mice were used. A dorsal skin graft measuring 2 $\times$ 3 cm was placed on the back of each recipient with the graft hair pointing in the opposite direction to that of the recipient hair. Donor and recipient were of the same sex. All recipients were 2 months old when grafted and the donors either 14 or 2 months old. Twelve months later 25 μ l. of acetone containing 40 μ g ml.⁻¹ of 7,12-dimethylbenz[*a*]anthracene (DMBA) was applied once to the depilated graft. The phase of the hair cycle was checked before treatment with DMBA by observing the growth (or absence of growth) of the hair stubs for 5 days after dyeing the hair. Papillomas first appeared on the grafts 4 weeks after the application of DMBA, and 3 weeks later the maximum number of papillomas had appeared. Approximately 60% of grafts from old donors and 25% of grafts from young donors bore papillomas (Table 1). Five months after DMBA treatment 80% of papillomas had regressed. Two months after the application of DMBA four carcinomas appeared on skin from an old donor and one on the skin from a young donor. No tumours developed on 35 male and 30 female mice bearing skin grafts treated with acetone only. This indicated an age dependent susceptibility of skin to a chemical carcinogen. The recipient mice were all of the same age, so that a decline in immune responsiveness with advancing age²⁻⁴ alone could not account for the difference in susceptibility of skin from old and young donors. Although the growth cycle of hair can greatly influence chemical carcinogenesis⁵⁻⁷, the number of mice in resting phase or growth phase was approximately the same in all groups, and I suggest that my results were not affected by this factor. The rate of skin sebum secretion may decrease with age and result in retention of a higher proportion of the applied carcinogen than in younger animals⁷. This may have increased the sensitivity of skin from old mice. It is unlikely to be the sole cause, as results have been obtained with lymphoid

Table 1 Papillomas on DMBA-treated Skin Grafts from Old and Young Syngeneic BALB/c Mouse Donors

Number of mice	Sex	Donor age when transplanted (months)	Graft age when DMBA treated (months)	Number of grafts in resting growth phase when DMBA treated	Number of papillomas	Number of carcinomas
24	M	14	26	12	12 (50%)	2
28	F	14	26	16	18 (64%)	2
15	M	2	14	7	2 (16%)	—
34	F	2	14	18	10 (29%)	1

tumours¹; lymphocytes transferred from old donors to young recipients resulted in a higher incidence of spontaneous lymphoid tumours than transfer from young donors.

My results suggest that the toxicity of a chemical carcinogen may differ to a degree, depending on the age of the tissue it contacts. The ages of those employed in potentially carcinogenic environments would have to be considered in greater detail if this is proved to be correct.

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Stereoselectivity and Differential Metabolism *in vivo* of Dextro and Laevo-Methadone-1-³H

MORPHINE-LIKE analgesics which exist as two or more optically active enantiomorphs are known to exert their pharmacological action exclusively or preponderantly in one

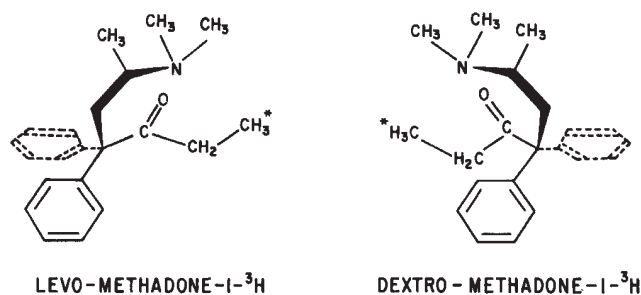


Fig. 1 Optical enantiomorphs of methadone. * Position of radio-label.

configuration¹. Dextro-isomers are generally inactive with respect to analgesia and effects on respiration and do not produce physical dependence in contrast to the pharmacologically active laevo-enantiomorphs. Optical isomers therefore have potential for the elucidation of basic mechanisms concerned with pharmacological effects. Previous studies on *d*- and *l*-isomers of methadone²⁻⁴ (Fig. 1), racemorphan⁵⁻⁷, zocine⁸, and prodine⁹ have not shown any meaningful delineations in absorption, regional distribution or metabolism of these isomers. Stereoselective events at the hypothetical asymmetric analgesic receptor have generally been postulated as the chief mediator of molecular specificity¹⁰⁻¹³. Together with previous work on *l*-methadone (refs. 14, 15 and A. L. M., S. J. M., J. R. Bloch and N. L. Vadlamani, submitted for publication) we show here for the first time that the observed enantiomeric potency differences between *d*- and *l*-methadone-1-³H could be attributed to (1) the formation of an apparently active metabolite in rat brain with *l*-methadone¹⁴, but not with *d*-isomer; (2) significant differences in half-lives of these isomers in rat brain and plasma; (3) differential stereoselective N-dealkylation pathway being a major route of metabolism with *l*- but not with *d*-isomer.

Male Wistar rats (110–150 g) were injected subcutaneously with a 10 mg kg⁻¹ dose of *d*-methadone-1-³H, approximate specific activity 6 μCi mg⁻¹ (New England Nuclear, Boston; radiochemical purity >99%; non-radioactive *d*-methadone carrier prepared as previously described¹⁶). They were lightly anaesthetized with ether and blood samples collected by intracardiac puncture in heparinized vacutainer tubes at set time intervals and immediately centrifuged for plasma. The brains were removed by decapitation and the concentration of drug in diluted 2 ml. aliquots of plasma or brain homogenates estimated as described for *l*-methadone¹⁴. The comparative mean values on distribution of dextro and laevo-methadone-1-³H in brain and plasma at different times and half-lives after a single subcutaneous injection are given in Table 1. Comparatively higher levels of *l*-isomer in rat brain were probably due to the higher lipid-solubility of this isomer (partition coefficients of *l*- and *d*-isomer in octanol/buffer, pH 7.4, were 57.3 and 28.3, respectively). The

Table 1 Comparative Distribution of Dextro and Laevo-Methadone-1-³H in Rat Brain and Plasma and Half-lives after a 10 mg kg⁻¹ (Free Base) Dose by Subcutaneous Injection

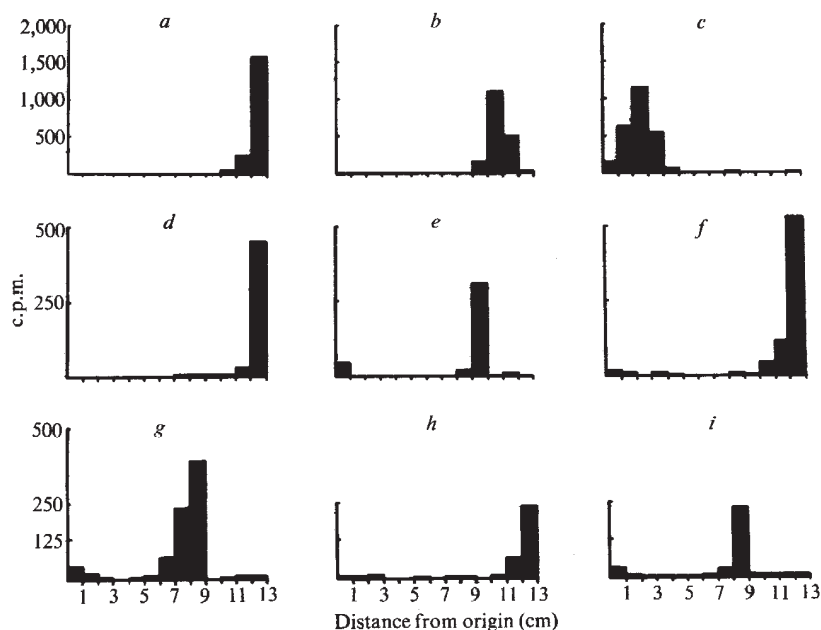
	0.5 h	1 h	2 h	6 h	12 h	24 h	48 h	1 week	3 weeks	Half-life* (h)
Laevo-methadone- ³ H-Brain	3,869	4,502	2,717	855	60	25	27	20	21	2.4
Plasma	1,798	1,400	1,479	645	38	17	—	—	—	3.7
B/P†	2.15	3.21	1.83	1.32	1.58	1.47	—	—	—	—
Dextro-methadone- ³ H-Brain	3,265	2,069	1,130	110	57	35	44	32	13	1.02
Plasma	536	417	278	43	15	6	3	—	—	1.5
B/P†	6.09	4.96	4.06	2.56	3.80	5.83	14.66	—	—	—

Data represent mean value (ng g⁻¹ wet brain weight or ng ml.⁻¹ plasma) of two animals for *d*- and four animals for the *l*-isomer at each time period.

* The half-lives were calculated from values on distribution of isomers up to 6 h.

† B/P represents the ratio of mean brain to plasma concentrations.

Fig. 2 Radioscans of thin-layer chromatograms (ITLC) of chloroform-isopropanol extract of rat brain 30 min after a 10 mg kg^{-1} subcutaneous injection of *d*-methadone- $1\text{-}^3\text{H}$. *a*, Silica gel, S_1 : ethyl acetate-methanol-ammonia (17:2:1, v/v); *b*, S_2 : solvent system: benzene-ethyl acetate-methanol-ammonia (80:20:1.2:0.1, v/v); *c*, ITLC alumina, S_3 : benzene-*n*-butyl ether (19:1, v/v); *d*, ITLC, silica gel, residue from 'Amberlite XAD-2' column, 30 min brains, system S_1 ; *e*, ITLC of *d* with system S_2 ; *f*, 6 h brains, residue from 'Amberlite XAD-2' column, ITLC, silica gel, system S_1 ; *g*, ITLC of *f*, system S_2 ; *h*, 12 h brains, residue from 'Amberlite XAD-2' column, ITLC silica gel, system S_1 ; *i*, ITLC of *h* with system S_2 .



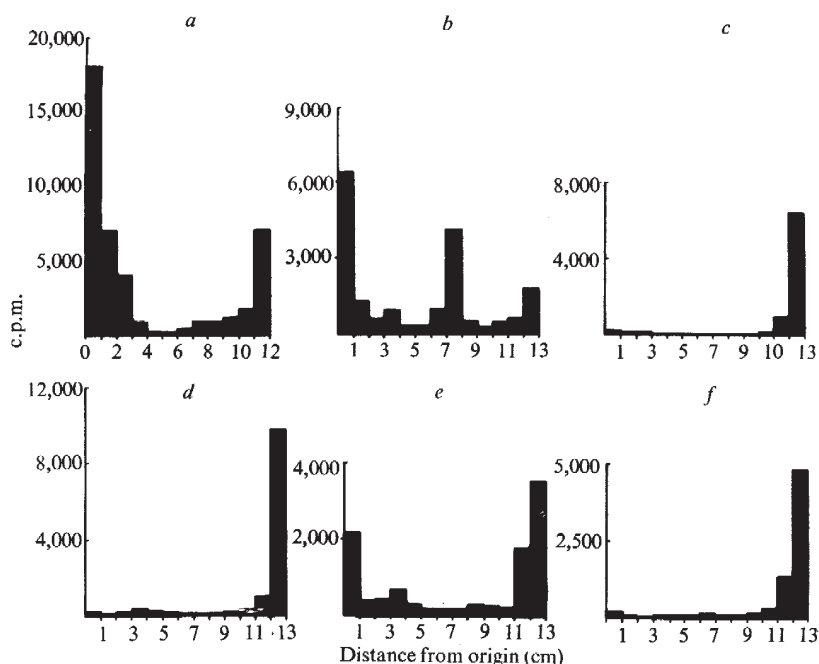
basic procedures for qualitative identification of *d*-methadone- $1\text{-}^3\text{H}$ in groups of four brains removed 0.5, 6 and 12 h after a single subcutaneous 10 mg kg^{-1} injection were similar to that described¹⁴ for *l*-methadone. The radioscans of thin layer chromatograms (Fig. 2) at these time periods showed a single peak of radioactivity due to *d*-methadone- $1\text{-}^3\text{H}$ in different solvent systems. In contrast, *l*-methadone scans¹⁴ consistently showed the presence of a metabolite in the brain in free form at the time of peak analgesia and as a protein-conjugate later in addition to free *l*-methadone. There were also marked differences in biologic half-lives of the isomers in rat brain and plasma at identical doses. Persistence of both free isomers in the rat brain and lack of striking differences in reversible protein binding of two isomers (ultrafiltration technique using 'Centriflo' membrane cones (Amicon Corp.) could account for the fact¹⁷ that the toxic actions and LD_{50} s of these isomers show no configurational discrimination by the intravenous or intraventricular route.

The mean values for free *d*-isomer excreted in rat urine and faeces 96 h following identical 10 mg kg^{-1} subcutaneous

doses were 8.29, 7.37%, respectively; total radioactivity, 15.99, 21.01%, respectively. Mean values for free *l*-isomer¹⁶ in urine and faeces were 11.31, 14.78%, respectively; total radioactivity 19.49, 29.8%, respectively.

Chromatography of the pooled filtered urine of rats given 10 mg kg^{-1} subcutaneous injection of *d*-methadone- $1\text{-}^3\text{H}$ on 'Amberlite XAD-2' eluted with methanol-ammonia (300:5) gave a residue, which was separated into methanol-soluble and insoluble fractions. The methanol-soluble fraction was further resolved on 'Gelman' ITLC into two subfractions using ethyl acetate-methanol-ammonia (17:2:1, v/v), polar metabolites, R_F 0.0 amounting to approximately 70% of total excreted urinary radioactivity and nonpolar metabolites, R_F 1.0 (Fig. 3a). (In the case of *l*-methadone- $1\text{-}^3\text{H}$, polar metabolites amounted to 22% of total urinary radioactivity¹⁶.) The nonpolar metabolites eluted from large ITLC sheets were resolved on ITLC using benzene-ethyl acetate-methanol-ammonia (80:20:1.2:0.1, v/v) into 4 metabolites, R_F 0.08, 0.27, 0.58, 0.96 with approximate distribution of radioactivity as 42, 10, 32 and 16%, respectively (Fig. 3b). These compounds were separately eluted

Fig. 3 Radioscans of ITLC from urine of rats given 10 mg kg^{-1} subcutaneous dose of *d*-methadone- $1\text{-}^3\text{H}$, processed on 'Amberlite XAD-2' resin: *a*, methanol-soluble fraction of residue from 'Amberlite XAD-2' column, with solvent system S_1 ; *b*, ITLC of subfraction R_F 1.0 of methanol-soluble fraction with system S_2 ; *c*, ITLC of polar subfraction R_F 0.0 of methanol-soluble fraction after enzymic hydrolysis in system S_1 ; *d*, ITLC of organic extract of acid-hydrolysate of R_F 0.0 subfraction, system S_1 ; *e*, ITLC of organic extract from *d* in system S_2 ; *f*, ITLC of extract from acid-hydrolysed methanol-insoluble residues from 'Amberlite XAD-2' column in system S_1 .



with methanol and characterized as *d*-methadone N-oxide (R_F 0.08), 2-ethylidene-1,5-dimethyl-3,3'-diphenyl pyrrolidine (R_F 0.27), *d*-methadone (R_F 0.58) and *p*-hydroxyphenyl derivative of *d*-methadone (R_F 0.96), respectively, by co-chromatography with authentic samples.

The polar fraction (R_F 0.0) proved to be predominantly glucuronide conjugates by enzymic hydrolysis with β -glucuronidase (Fig. 3c). Acid-hydrolysis of conjugates and subsequent extraction with chloroform-isopropanol (3:1, v/v) and ITLC with ethyl acetate-methanol-ammonia (17:2:1, v/v) (Fig. 3d) and with benzene-ethyl acetate-methanol-ammonia (80:20:1.2:0.1, v/v) (Fig. 3e) showed the formation of *p*-hydroxyphenyl *d*-methadone N-oxide (R_F 0.04), *p*-hydroxyphenyl pyrrolidine derivative (R_F 0.27), *d*-methadone (R_F 0.68), and *p*-hydroxyphenyl *d*-methadone (R_F 0.96) with approximate distribution of radioactivity as 25.3, 14.3, 5.7, and 54.7%, respectively (Fig. 3e). Acid hydrolysis of the methanol-insoluble residue of the eluate from 'Amberlite XAD-2' column, extraction and ITLC of extract with ethyl acetate-methanol-ammonia (17:2:1, v/v) (Fig. 3f) and subsequent resolution with system: benzene-ethyl acetate-methanol-ammonia (80:20:1.2:0.1, v/v) provided a pattern of metabolites identical to that given in Fig. 3e.

The major metabolic pathways for *d*-methadone with qualitative similarity to *l*-isomer¹⁵ are: (a) *p*-aromatic hydroxylation by hepatic microsomal mixed-function oxidase system which has a low order of substrate specificity, (b) glucuronide conjugation, and (c) N-oxidation¹⁸. By contrast with *l*-methadone only minor amounts of pyrrolidine^{19,20} and *p*-hydroxyphenyl pyrrolidine metabolites²¹ were formed; thus mono-N demethylation and subsequent cyclization are a very minor metabolic route in *d*-methadone. These *in vivo* findings with *d*-methadone are consistent with earlier observations from *in vitro* liver microsomal^{22,23} and isomeric substrate studies²⁴ where the active *l*-isomer was shown to be more readily N-dealkylated than inactive *d*-isomer, and N-dealkylation rather than N-oxidation was shown to be stereoselective.

These observations on comparative metabolism *in vivo* of optical enantiomorphs of methadone-1-³H at identical 10 mg kg⁻¹ subcutaneous doses strongly suggest that (1) the stereoselective N-demethylation pathway as previously postulated¹⁴ is a preferential route with active *l*-isomer; (2) significant differences exist in half-lives of isomers in plasma and brain; and (3) the formation of an apparently active metabolite in rat brain occurs with *l*-isomer¹⁴, but not with *d*-isomer.

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Milk Proteins: Reply

WE are grateful to Dr Wheelock¹ for drawing our attention to some mistakes in our paper². The α_2 -casein was inadvertently labelled α -casein and in error had been included as a glycoprotein, which it is not. This correction, which reduces the percentage of milk proteins which are glycosylated, further emphasizes the wider argument presented in the paper, based on various analyses of which bovine milk is only one, that extracellular proteins do not, of necessity, require glycosylation for export from the cell.

With regard to the other points raised, K-casein referred to in refs. 3 and 4 is the monomeric reduced form, not the native disulphide bridged polymer. Although only 28% of monomeric K-casein is glycosylated⁴, the situation concerning the polymer is uncertain. We did not list α -lactalbumin as a glycoprotein because the glycosylated form (the existence of which was stated) accounts for less than 10% of the total α -lactalbumin in bovine milk.

The role of the carbohydrate moiety of K-casein in the interactions of the caseins has not been resolved yet by the workers in this field. Lysozyme, a glycosidase, has a similar coagulation action on casein micelles to that induced by rennin⁵, while Talbot and Waugh⁶ related the stabilizing capacity of K-casein to the content of one of the carbohydrates, N-acetylneuraminic acid. Even the critic of our paper has expressed the opinion that the rate of action of rennin is influenced by the nature of the saccharide unit⁷. Therefore, on the evidence available the use of K-casein as an example of anti-recognition is not invalid.

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Relation between Glucose Absorption Rate and Serum Globulin Concentration in Man

GLUCOSE absorption rate has been shown to be depressed in patients with acute and chronic systemic bacterial infections¹. Similarly, the weight of D-xylose excreted after an oral load is decreased in such patients², probably also as the result of impaired absorption. The cause of these abnormalities is unknown and they are not due to a change in jejunal morphology. Whether systemic parasitic infestations also lead to an impairment of monosaccharide absorption has not been investigated in man.

Eighteen Zambian African subjects, all in-patients at the University Teaching Hospital, Lusaka, from many Zambian tribes³, were studied. The purpose of the investigation and the experimental procedure were explained. They had been admitted with a wide variety of diagnoses, but in none was there clinical evidence of an infection, malnutrition or gastro-intestinal disease. Results for glucose absorption rates in thirteen of them have previously been reported⁴⁻⁶. Eleven were men and seven women. The mean age was 37 (16-61) years, and mean body weight 55 (43-79) kg. Mean haemoglobin concentration was 12.5 (3.9-17.0) g 100 ml.⁻¹. Total serum protein was estimated by a modification of the biuret method⁷, and electrophoresis was done using a 'Beckman R-101' microzone cell. All determinations were made in duplicate and standard curves using 'Wellcomtrol' assayed serum 'MR 82' (Wellcome Reagents Ltd, Beckenham, Kent) were constructed. Mean albumin was 3.4 (2.4-4.4) g 100 ml.⁻¹. Mean α_1 , α_2 , β and γ -globulin were 0.3 (0.2-0.4), 0.9 (0.4-1.4), 1.0 (0.8-1.2) and 2.1 (1.4-2.9) g 100 ml.⁻¹ respectively; 5 h D-xylose excretion was estimated in four after a 25 g oral load², and was 5.2-6.4 (mean 5.7) g. Stool parasites were found in one out of thirteen (hookworm ova). Jejunal biopsy specimens were obtained from three subjects which were normal by dissecting-microscope and routine histological techniques⁸. The technique for measuring glucose absorption rate has been described previously^{1,4}. A double-lumen tube was positioned in the proximal jejunum and the tests were performed after a 14-18 h overnight fast. A solution containing 200 mmol l.⁻¹ glucose, 100 mmol l.⁻¹ sodium chloride, and 0.50 g 100 ml.⁻¹ polyethylene glycol 4,000 was pumped at a constant rate of 12.0 ml. min.⁻¹ through a proximal opening, and intestinal content was collected from

a distal opening into the other lumen 30 cm further along the jejunum by siphonage. The mean distance of the proximal opening past the duodeno-jejunal flexure was 15 (1-38) cm. Three 10-min collections of fluid were obtained after an equilibration period of 35 min. Laboratory methods and calculation of absorption rates were as previously described^{1,4}.

The mean glucose absorption rate for the eighteen subjects was 0.23 (0.15-0.35) g min.⁻¹ 30 cm of jejunum.⁻¹; the inverse correlation between absorption rate and tube position was significant ($r = -0.51$; $P < 0.05$). As well as analysing data from the eighteen subjects together, we considered separately, those obtained when the infusion was made at < 20 cm (mean 8 (1-18) cm; $n = 11$), and > 20 cm (mean 26 (22-38) cm; $n = 7$) distal to the duodeno-jejunal flexure. The correlations between individual absorption rates and total and γ -globulin concentrations were inversely significant for all subjects ($r = -0.58$; $P < 0.02$, and $r = -0.62$; $P < 0.01$), and also for those in whom the infusion was made at < 20 cm past the duodeno-jejunal flexure ($r = -0.62$; $P < 0.05$ and $r = -0.74$; $P < 0.01$). Fig. 1 shows the association between individual absorption rates and serum γ -globulin concentrations. There was no significant correlation between absorption rate and age, body weight, haemoglobin, albumin or α_1 , α_2 , and β -globulin concentrations. The absorption rates in the subjects who had xylose tests were 0.35, 0.27, 0.27 and 0.15 g min.⁻¹ 30 cm of jejunum.⁻¹. The three subjects who had jejunal biopsy specimens examined had absorption rates of 0.27, 0.27 and 0.15 g min.⁻¹ 30 cm of jejunum.⁻¹.

An inverse association between serum total and γ -globulin concentrations and glucose absorption rate from a 200 mmol l.⁻¹ glucose solution has been demonstrated. The cause of the high globulin in some of the subjects, none of whom had clinical evidence of an infection, is unknown. Malaria, schistosomiasis and helminthiasis were probably responsible for most. The present data show that a small rise in γ -globulin concentration can be associated with a marked impairment in absorption rate (Fig. 1). There was no significant association between absorption rate and serum albumin concentration. Falaiye⁹ has suggested that hypoalbuminaemia is important in the aetiology of malabsorption in asymptomatic Nigerians. In that study, although improved absorption followed a rise in albumin, the total globulin concentration fell markedly during the period of investigation. Malabsorption of fat and xylose has been demonstrated in some patients with active rheumatoid arthritis¹⁰. It seems from that and the present study that a high serum globulin concentration in inflammatory and infective disease is associated with an impairment of absorption, even though the jejunum is morphologically normal.

Glucose absorption in Zambian African subjects takes place over a relatively short length of proximal jejunum, and little transfer seems to occur distally (Cook and Snook, unpublished). In the eighteen subjects in the present study there was a significant inverse relation between absorption rate and tube position which, however, did not influence the conclusion.

A previous study has shown a significant correlation between glucose absorption rate from a 30 cm jejunal segment and 5 h D-xylose excretion after a 25 g oral load¹. It therefore seems possible that there is a significant impairment of monosaccharide absorption from the diet of subjects with chronic infections. Parasitic diseases are extremely common in developing areas of the world. It seems probable that sub-clinical malabsorption is a common sequel.

I thank Mr James Tembo for his help with the patients and Mr R. W. Wenlock for the serum protein electrophoresis determinations. Dr N. O. Berg examined the jejunal biopsy specimens. The investigation was supported by the University of Zambia Research Fund.

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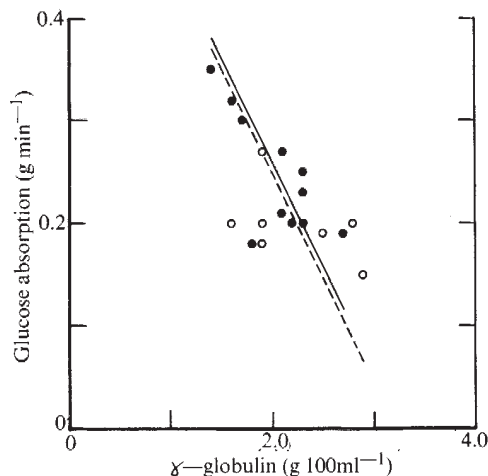


Fig. 1 Correlation between glucose absorption rate (g min.⁻¹ 30 cm of jejunum.⁻¹) and serum γ -globulin concentration (g 100 ml.⁻¹). In the subjects in whom the infusions were made at less than 20 cm distal to the duodeno-jejunal flexure (●) the correlation is inversely significant ($P < 0.01$); the equation for the calculated regression line (—) is $x = 3.25-4.89$ y. When data from all of the subjects are included in the analysis, the correlation is also inversely significant ($P < 0.01$); the equation for the calculated regression line (---) is $x = 3.23-4.93$ y.

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Neural Control on the Activity of the Calcium-transport System in Sarcoplasmic Reticulum of Rat Skeletal Muscle

IF the normal nerve supply to a slow skeletal muscle is replaced by a foreign, fast motor innervation, its isometric twitch response is speeded up, to resemble that of a fast muscle¹⁻⁴. In cross-innervated rat soleus, the molecular basis for this transformation has been located to an effect on the molecular properties of myosin. The reduction in twitch contraction-time was found to be associated with coordinate increases of the maximum speed of shortening and of myosin ATPase activity^{5,6}. In similar experiments with cat soleus, however, both the maximum contraction velocity and the ATPase activity of isolated myosin were only slightly changed under the experimental conditions⁶⁻⁸. Demonstration of an enhanced maximum capacity for accumulation of Ca²⁺ in the isolated sarcoplasmic reticulum from cat reinnervated soleus led to the alternative suggestion that fast innervation to a formerly slow muscle accelerated the time-course of the active state by increasing the rate of translocation of Ca²⁺ from the myofibrils into the lumen of the intact sarcoplasmic reticulum^{8,9}.

This hypothesis, because of its wider implications concerning a rate-limiting role of intracellular Ca²⁺ passage on the muscular contraction-relaxation cycle, requires two conditions. First, a conditional expression of the activity of the membrane-bound Ca²⁺-transport system of reticular membranes by fast motor innervation must be more definitely proven; second, that the effect is verified in reinnervated slow muscles from mammalian species other than the cat.

The sciatic nerve of young adult male Wistar rats was severed on one side, and conditions arranged to promote reinnervation of the soleus muscle from the regenerating nerve stump, as described by Miledi and Stefani⁴. The process was completed in three to four months, when the reinnervated muscles had reached an average fresh weight of about 100 mg and about 70% of that of the contralateral, unoperated muscles. The effects of this operative procedure were shown to be similar to those after cross-innervation regarding twitch contraction time of the reinnervated soleus⁴.

In our experiments, the paired, operated and contralateral muscles from eight to ten rats were separately pooled and the tissue homogenates, prepared in 0.3 M sucrose, were fractionated by differential centrifugation¹⁰. Isolation and purification of myosin from the crude myofibrillar sediment was identical to that described previously¹⁰. In our experiments, the myosin from the reinnervated soleus had a mean ATPase activity of 0.36 ± 0.08 and 1.22 ± 0.21 $\mu\text{mol P}_i \text{ min}^{-1} \text{ mg}^{-1}$ protein, with Ca²⁺ and EDTA as the respective activators^{10,11}, as compared with control values of 0.24 ± 0.05 and 0.86 ± 0.10 . The rate of ATP hydrolysis by myosin therefore appeared to be enhanced after changing the nerve supply to the muscle, but did not reach the high values found with purified myosin from the fast muscle, normal extensor digi-

torum longus (0.69 ± 0.10 and 2.42 ± 0.23 $\mu\text{mol P}_i \text{ min}^{-1} \text{ mg}^{-1}$ protein for Ca²⁺-activated and EDTA-activated ATPase activities, respectively). Sciactectomy and subsequent reinnervation of soleus was less effective in the change of myosin from a "slow" to a "fast" molecular form than cross-innervation, by which an almost complete transformation of myosin has been obtained^{5,6}.

Table 1 Biochemical Transformation of Isolated Sarcoplasmic Reticulum from Rat Soleus Induced by Foreign Motor Innervation

	Control soleus	Reinnervated soleus
Ca ²⁺ -uptake, initial rate	0.10 ± 0.02	0.23 ± 0.03
EGTA-sensitive, Mg ²⁺ , K ⁺ ATPase activity	0.19 ± 0.09	0.35 ± 0.09
Rotenone-insensitive, NADH-cytochrome c reductase activity	85 ± 9	86 ± 12

Activities are expressed as μmol of Ca²⁺ accumulated and P_i formed, or nmol of cytochrome c reduced, per min per mg of microsomal protein, and were measured by methods described by Margreth *et al.*¹⁰. Mean values are reported $\pm$ s.e.m. (number of determinations in parentheses) of paired determinations on reinnervated and contralateral muscles. The mean Ca²⁺-uptake activities of sarcoplasmic reticulum preparations from normally innervated slow soleus and fast-extensor digitorum longus of rats, obtained from the pooled data of these and other experiments were 0.10 ± 0.01 (18) and 0.37 ± 0.05 (7), respectively.

Concomitant changes in the enzymic composition of sarcoplasmic reticulum fragments isolated from soleus were also recorded. The results in Table 1 show that the modifications induced by the foreign innervation to slow muscle were selective to the membrane-bound Ca²⁺-transport system. The specific activity of the rotenone-insensitive NADH-cytochrome c reductase, electron transport chain was virtually unchanged, and it did not deflect from the relatively high values found in slow as compared with fast muscles¹². The increased Ca²⁺-uptake activity of the sarcoplasmic reticulum from reinnervated soleus was due to an effect on the Ca²⁺-transport system itself, rather than just reflecting an increased Ca²⁺-accumulating capacity of the microsomal vesicles. Thus the increase concerned the initial rate of Ca²⁺-accumulation and paralleled that of the Ca²⁺-transport, EGTA-sensitive ATPase¹⁰ activity.

A phosphorylated protein intermediate was implicated in the ATPase reaction of the sarcoplasmic reticulum, and the extent of phosphorylation of membrane preparations isolated from reinnervated soleus and the contralateral soleus and extensor muscles was assayed¹³ using ATP labelled terminally with ³²P. The steady-state concentrations of phosphorylated intermediate, expressed as nmol ³²P incorporated mg⁻¹ protein, were, in the stated order, 0.40, 0.25 and 0.87, in good agreement with the ATPase and Ca²⁺-uptake measurements. Most of the phosphorylation was due to an increased amount of the ATPase enzyme concerned with Ca²⁺-transport, which appeared to be supported by results obtained from polyacrylamide-gel electrophoresis^{10,14} of the same preparations. The electrophoretic patterns in Fig. 1 show that the relative proportion of a distinct protein species of low mobility currently identified with the ATPase enzyme¹⁰, in the fraction from the reinnervated muscle, was intermediate between that found in the homologous fractions from slow muscle and fast muscle (Fig. 1). In spite of the transformation in protein composition of reticular membranes, corresponding to a slow to fast change, some of the fast-moving electrophoretic components characteristic of the rat soleus microsomes persisted after reinnervation. Conversely they were virtually absent in the homologous fraction from fast extensor¹⁰ (Fig. 1).

We suggest that coupled changes in the isoenzyme composition of myosin, and in the macromolecular composition of reticular membranes, cooperate to the transformation of the twitch characteristics of rat soleus after sciactectomy and the

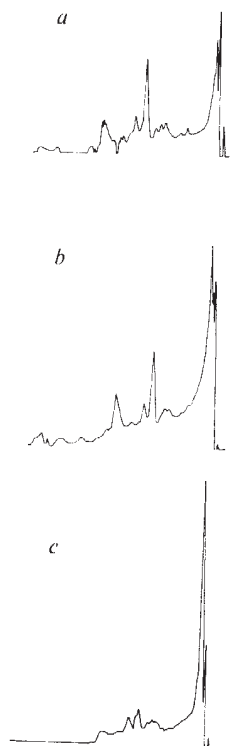


Fig. 1 Polyacrylamide-gel electrophoresis patterns and densitometric records (left side, at reduced scale) of sarcoplasmic reticulum protein from normally innervated, slow soleus (*a*), fast extensor (*c*) muscles and reinnervated soleus (*b*). Gel electrophoresis was carried on about 50 μ g of protein, under conditions identical to those described previously¹⁰, by the method of Panet and Selinger¹⁴. Migration was towards the cathode (3 mA gel⁻¹ for 3.5 h). The gels, after staining with 'amido black', were scanned at 620 nm in a 'Gilford recording spectrophotometer'.

subsequent reinnervation from predominantly fast nerve fibres⁴. The concept that the activity of the reticular Ca^{2+} -transport system is specified by epigenetic mechanisms linked to the pattern of impulses from the motor innervation^{8,9} to the muscle might be clarified at the molecular level, in terms of a neural control on the synthesis and/or assembly of the transport ATPase into the reticular membranes. The selective accumulation of this catalytic protein in the sarcoplasmic reticulum of rat reinnervated soleus might be equivalent to a permanent derepression, after the loss of a negative feedback control from the original innervation to this muscle, which is supported by acute denervation experiments¹⁰.

Some of these results were given at the 2nd International Congress on Muscle Diseases (Perth, November 1971). We thank the Muscular Dystrophy Associations of America for financial support and Mr R. Siligardi for technical help.

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Retention of Pacemaker Activity in Mammalian Myocardial Cells recovered from Liquid Nitrogen

SUCCESSFUL preservation of the mammalian heart in the frozen state is not yet possible because of the sheer bulk of the organ as well as difficulties at the cellular level¹. Pacemaker activity must be retained, however, and so I have made preliminary studies of sustained rhythmic contractions in dissociated cells. A pacemaker cell in culture is one which, although isolated from contact with neighbours, beats rhythmically². A method for freeze-preservation of sheets of beating rat myocardial cells and myocardial cells frozen in suspension has been described³, using dimethyl sulphoxide as a cryoprotective agent, in which resumption of contractility was observed on thawing. Estimates of restoration, however, were made on dense populations of cells in confluent sheets, which would be expected to produce a high proportion of beating cells, as myocardial cells capable of pacemaker activity can drive responsive neighbours with which they may come in contact⁴.

I report here on the survival of pacemaker activity in isolated mammalian myocardial cells frozen in liquid nitrogen, using ethylene glycol as the cryoprotective agent. A successful penetrating cryoprotective agent must enter the cell freely to avoid producing osmotic dehydration, and it must be non-toxic in the high concentrations necessary to protect against freezing injury⁵. Studies of potential cryoprotective agents have demonstrated toxicity in all but glycerol and ethylene glycol^{6,7}. Ethylene glycol can penetrate membranes far more quickly than glycerol^{8,9}, producing less osmotic stress, so it is the most obvious choice for investigations on the freeze-preservation of mammalian myocardium.

Cultures of foetal rat myocardial cells derived by trypsinization of whole foetal hearts⁸ were suspended in growth medium containing 2.5 M ethylene glycol or 2.5 M glycerol or 2.0 M dimethyl sulphoxide. Suspensions containing 10^6 cells ml.⁻¹ in 2 ml. glass ampoules were cooled to -196°C at 2° to 3° per min. After storage in liquid nitrogen for 24 h, the ampoules were warmed to 37°C at 200°C per min and the cells placed in growth medium where the cryoprotective agent was diluted to 0.1 M. After 30 min the cells were removed by centrifugation and allowed to settle on glass cover slips. Known volumes of cell suspension were placed over known areas of cover slip, and control cultures were prepared by using equal volumes of unfrozen cell suspension on equal areas of cover slip. Survival was measured 24 h later by counting the total number of isolated cells and the number of isolated beating cells per unit area in the controls, and comparing these with the numbers derived from cultures previously frozen.

The results are shown in Table 1. Ethylene glycol appeared preferable but the recovery of pacemaker activity was low; this may reflect a selective destruction of pacemaker cells, or, perhaps more likely, a failure to resume contractions by some cells which were pacemakers prior to freezing. Cells in suspension may not recover easily from freezing injury because they are still suffering from trypsinization^{10,11}.

Table 1 Cells Frozen in Suspension

Cryoprotective agent	Surviving intact myocardial cells (% of controls after freezing)	Pacemaker cells (% of total population)		Calculated % retention of pacemaker activity after freezing
		Before freezing	After freezing	
2.5 M ethylene glycol	62±5	30±3	19±6	63
2.5 M glycerol	7±2	28±4	Nil	Nil
2.0 M dimethyl sulphoxide	58±5	23±6	4±2	17

Values are means ± s.e. from five separate experiments.

I studied cells which had attached to cover slips for 40 h prior to freezing and thawing. The same conditions of control applied as before, except that control cultures were passed through medium containing 2.5 M ethylene glycol before reincubation, to allow for cells which became dislodged on handling. Cover slip cultures in 2.5 M ethylene glycol were cooled and warmed at the same rates as before, and survival was measured 24 h after thawing. Table 2 illustrates the improvement in restoration of pacemaker activity.

Table 2 Cells Frozen on Cover Slips

Cryoprotective agent	Surviving intact myocardial cells (% of controls after freezing)	Pacemaker cells (% of total population)		Calculated % retention of pacemaker activity after freezing
		Before freezing	After freezing	
2.5 M ethylene glycol	59±5	39±5	40±3	100

Values are means ± s.e. from four separate experiments.

Cells in suspension survive freezing in dimethylsulphoxide to the same extent as in ethylene glycol. More than 80% of the pacemaker population, however, failed to resume beating after exposure to dimethyl sulphoxide, which probably reflected the toxicity of this compound^{6,7}. Glycerol, although non-toxic^{8,9}, failed to protect myocardial cells to any great extent, probably by its failure to penetrate cells easily and quickly^{8,9}, so causing lethal osmotic stress.

Cells attached to a surface clearly responded differently to cells frozen in suspension. This may be because they have recovered from trypsinization, in which case they surely provide a more realistic model for studies designed as a prelude to work with whole organs.

The choice of ethylene glycol as a suitable penetrating cryoprotective agent for myocardial cells, based on studies of toxicity and permeability⁶⁻⁹, has been confirmed. Frog hearts, cooled to -78°C in the presence of multi-molar concentrations of ethylene glycol, resumed spontaneous contractions for a short time when re-warmed¹², and preservation of whole mammalian hearts could in future be attempted using such compounds.

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Cigarette Smoke: Effect of Aqueous and Nonaqueous Fractions on Mitochondrial Function

TOBACCO smoke or components exert inhibitory effects on respiratory cilia¹ and the ciliary activity of *Paramecium*²⁻⁴. Kennedy and Elliot⁵ observed that in *Tetrahymena* tobacco smoke caused structural alteration in the inner mitochondrial membrane followed by the cessation of ciliary activity, attributed to a block in the energy generation process in mitochondria. Because the latter are the primary sites of energy production in an aerobic cell, we studied the effects of tobacco smoke components on mitochondrial function. Effects of aqueous and nonaqueous fractions from whole smoke of tobacco on mitochondrial respiration and coupled energy generation were examined.

Rat liver mitochondria were isolated according to the method of Schneider⁶. Oxygen uptake was measured polarographically by a Clarke-type platinum oxygen electrode. Reaction mixture in a final volume of 3.0 ml., containing mannitol 0.21 M, sucrose 0.07 M, Tris-HCl 0.02 M, EGTA 0.02 mM, P_i 5 mM, and MgCl₂ 3 mM (final pH 7.2), was saturated with air at 30°C before the addition of oxidizable substrates. To determine the effect of tobacco smoke components, various quantities of the fractions were pre-incubated for 3 to 5 min in the reaction mixture containing mitochondria (1 mg protein ml.⁻¹) before the addition of substrates for O₂ uptake. The State 3 and State 4 respiration rates, respiratory control ratios and ADP:O ratios were obtained by the method of Chance and Williams⁷.

Aqueous (W/S) and nonaqueous (W/Ins.) fractions from tobacco smoke were supplied by Dr John Benner and were prepared under standard conditions (35 ml. puff volume, 2 s puff duration and 1 puff per min) by the Core Service Facility of the University of Kentucky Tobacco and Health Research Institute. IRI research cigarettes were smoked with a Heiner-Borgwaldt smoking machine and the fraction of the whole smoke was collected directly in precooled water at 0°C, using a pump on a 'Chemap Vibromixer'. A 5 ml. aliquot of the aqueous solution containing the W/S fraction was evaporated to dryness under vacuum and the dry weight of the residue determined. On the basis of this a 50 mg dry wt residue ml.⁻¹ solution of W/S fraction was prepared. The W/Ins. fraction of whole smoke settled on the glass vessel walls and was collected in acetone and evaporated to dryness. The residue was weighed and a 50 mg ml.⁻¹ DMSO solution prepared. Comparable volumes of DMSO were added to mitochondrial preparations in control experiments.

Both W/S as well as W/Ins. fractions from tobacco smoke inhibited the State 3 respiration of freshly isolated mammalian mitochondria to varying degrees depending upon the concentration of the fraction and the type of substrate employed (Fig. 1 and Table 1). The W/S fraction also inhibited the State 4 respiration of mitochondria but low concentrations of W/Ins. fraction stimulated it. The O₂ uptake by mitochondria with β -hydroxybutyrate (β -HB), a pyridine nucleotide-linked substrate, was less sensitive to W/S fraction than respiration with succinate. The W/Ins. fraction, on the other hand, inhibited β -HB oxidation more

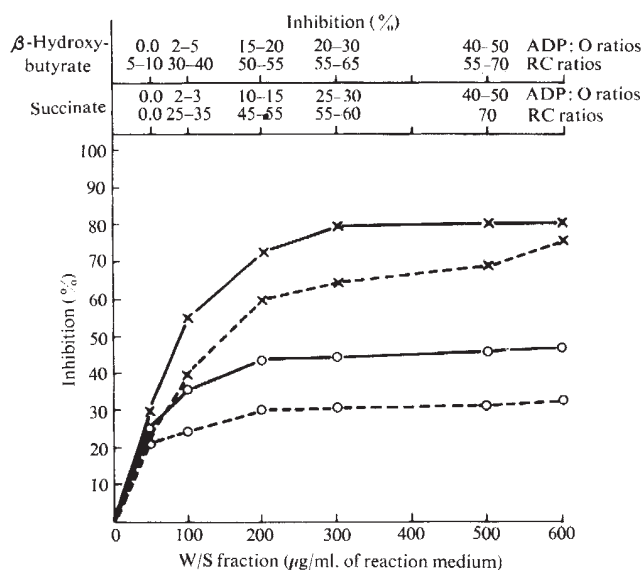


Fig. 1 Effect of aqueous fraction W/S on mitochondrial respiration. W/S fraction from whole smoke of IRI-UK research cigarettes. Oxygen uptake rates recorded after 3–5 min preincubation of rat liver mitochondria in the presence of aqueous fraction. $\times$ — $\times$, Succinate substrate, State 3; $\times$ --- $\times$, β -hydroxybutyrate substrate, State 3; $\circ$ — $\circ$, succinate substrate, State 4; $\circ$ --- $\circ$, β -hydroxybutyrate substrate, State 4.

than succinate oxidation. Almost complete inhibition of the oxygen uptake occurred in presence of 400–600 μg of W/Ins. residue, but complete inhibition of respiration could not be obtained even in the presence of 1,800 μg of W/S residue.

Respiratory control and ADP:O ratios gradually declined upon treatment of mitochondria with W/S fraction (Fig. 1). In the presence of low concentrations of W/Ins. fraction, respiration control was lost with a simultaneous loss in the ADP:O ratios.

It has been suggested that inhibition of oxygen uptake by lung tissue homogenates and excised lungs on exposure to tobacco smoke is due to inhibition of the mitochondrial system⁸. Our results show that very small amounts of tobacco smoke fractions cause inhibition of mitochondrial respiration. Partial insensitivity (about 20%) of active respiration to high concentrations of W/S fraction (Fig. 1) compared to complete inhibition by W/Ins. fraction (Table 1), and a differential susceptibility of β -HB and succinate oxidation, suggest a different mode of action for the two fractions and a differential sensitivity of mitochondrial respiration with the two substrates. Appreciable stimulation of State 4 respiration by small quantities of W/Ins. fraction indicates the presence of compounds similar to uncoupling agents of mitochondrial oxidative phosphorylation.

Table 1 Effect of Nonaqueous Fraction W/Ins. on Mitochondrial Respiration

Substrate	Conc. (μg ml^{-1})	State 3	State 4	
		respiration Inhibition %	respiration Inhibition %	Stimulation %
Succinate	25	9.0	—	59.0
	50	32.0	—	87.0
	100	63.0	—	47.0
	200	79.0	3.0	—
β -Hydroxy- butyrate	25	29.0	—	13.0
	50	46.0	—	62.0
	100	81.0	12.0	—
	200	97.0	94.0	—

W/Ins. fraction from whole smoke of IRI-UK research cigarettes dissolved in DMSO. Oxygen uptake rates were recorded after 3–5 min preincubation before addition of substrate.

Kennedy and Elliot⁵ found the gaseous phase (which is probably equivalent to our W/S fraction) is ciliostatic and caused swelling of mitochondria, but did not disrupt inner mitochondrial membrane. The particulate phase or residue, which is probably equivalent to our W/Ins. fraction, caused a disruption of the inner mitochondrial membrane suggesting a block in energy generation resulting in ciliostasis. Our results show that both fractions cause a decline in energy generation by mitochondria. If ciliostatic activity results from impaired energy generation then both the gaseous as well as the particulate phases of cigarette smoke are involved in ciliostasis due to their ability to inhibit oxidative phosphorylation.

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Changes in Critical Flicker Frequency during and after Fourteen Days of Monocular Deprivation

ALTHOUGH the technique of monocular occlusion has long been used by ophthalmologists¹ in the therapeutic treatment of such conditions as strabismus (squint) and amblyopia, particularly in young children, little experimental work has been directed at determining the nature of visual sensitivity in the nonoccluded eye. Will this eye show a compensatory improvement in acuity as a result of prolonged disuse of the other eye, and, if it does, will this effect dissipate with time following removal of the occluding eye patch? In an attempt to throw some light on this important applied and theoretical problem we have recently conducted a series of studies² in which the critical flicker fusion frequency (CFF), a measure of temporal visual acuity, was determined in adult subjects, with normal vision, at periodic intervals during 7 days of monocular deprivation. No significant changes in the CFF of the occluded eye were observed. The temporal pattern of the nonoccluded eye, however, was characterized by an initial decrease in the CFF at 3 and 6 h (that is, poorer acuity), a reversal to the pre-experimental baseline at 9 h, and then a negatively accelerating improvement in performance as a function of monocular deprivation duration. This temporal pattern occurred regardless of whether the dominant or nondominant (weak) eye was occluded. Furthermore, these results were only obtained if a black rather than a white translucent eye patch was used, a finding which indicates that our monocular phenomenon was produced by an absence of visual stimulation *per se* and not by an absence of pattern vision.

In this study, in which the duration of monocular deprivation was extended by 7 days and a 14-day follow-up period was introduced, we wished to determine whether the performance of the nonoccluded eye would continue to improve during the second week or whether it would begin to decline towards the baseline level, an effect which might occur as a result of the subject's adaptation to the novelty of the experimental condition. Contrary to our expectations, we report

a "step-like" increment in CFF performance on day 11, an improvement that occurred after a plateau had been reached on days 7 and 9. We also report that this visual improvement is of a long lasting nature, being present to some degree, in most subjects, 14 days after removal of the eye patch.

Sixteen male university students, all with normal vision, were divided into an experimental and a control group, each containing eight subjects. The experimental subjects were required to live for 14 days in a large furnished room (3.66 m × 14.02 m) which contained a radio, a television set, reading material and a variety of games. The subjects were confined to these quarters in groups of four, each subject wearing a black patch over the dominant eye for the entire duration. The CFF, taken only from the nondominant test eye (the nonoccluded eye), was determined before the application of the patch (day 0) and then at intervals of 1, 3, 5, 7, 9, 11 and 14 days of monocular deprivation. Subsequently, the patch was removed and the subjects were allowed to go home. However, they were required to return to the laboratory periodically for follow-up tests, the CFF being taken from the test eye on postocclusion days 1, 3, 5, 7 and 14. Each test session, conducted between 0830 h and 0930 h, was preceded by a meal and 15 min of dark adaptation. During the confinement period, only the test eye was dark adapted since the other eye was already occluded while in the post-confinement period both eyes were dark adapted. These results were then compared with those derived from the corresponding eye (nondominant) of eight non-confined controls who were tested at the same time of the day and at the same time intervals as the experimental group. (A confinement control group was not used since we have already demonstrated that a prolonged period of confinement *per se* does not affect the CFF.)

The stimulus consisted of a white light, at an initial flicker frequency above fusion, which was presented monocularly by a cold cathode modulating lamp mounted at the rear of a standard viewing chamber (Lafayette, model 1202C). The angle subtended by the centrally fixated stimulus was 2°10', a value assuring full foveal stimulation. The flicker-generating apparatus (Grason-Stadler, model E622) was set at a light-dark ratio of 0.50 and a lamp current reading of 22.6 mA. Eight trials were presented to the nondominant eye at each test period. The descending method of limits was used, the subject's task being to report the first indication of flicker. The arithmetic mean of these eight trials was taken as the descending monocular CFF threshold.

As Fig. 1a shows, there was a negatively accelerating improvement in the CFF of the nonoccluded eye up to day 7, a plateau from days 7 to 9, a "step-like" improvement at day 11, and, finally, after the removal of the eye patch, a gradual decline towards the pre-experimental baseline. On the other hand, the CFF of the corresponding eye of the control group showed no systematic changes during the entire 28-day test period. An analysis of variance (mixed design for repeated measures⁹) revealed a significant difference between the two groups ($F=6.49$; $P<0.02$), a significant change over days ($F=10.42$; $P<0.001$), and a significant interaction effect ($F=9.63$; $P<0.001$). Subsequently, a series of individual two-tailed t tests were performed comparing the relative performance of the two groups at the various test periods. This analysis revealed a significant difference at all test periods (P values <0.01), except at day 0, during the 14-day occlusion period. In addition, the increment from days 9 to 11, relative to the plateau from days 7 to 9, was also statistically significant ($P<0.01$).

The results of the follow-up tests indicated the presence of significant after-effects on postocclusion days 1 and 3 (P values = 0.05) but not on the subsequent days. In spite of this statistical finding, it is important to note that six of the eight subjects, all of whom showed a gradual decline in performance, still had not reached their individual baseline level on day 14, a finding which suggests that these after-

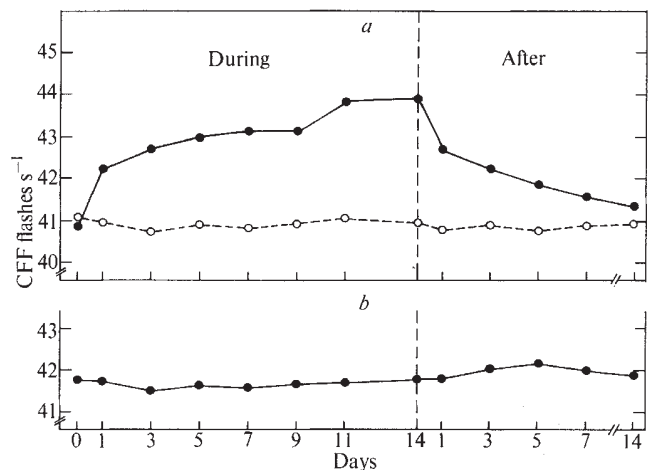


Fig. 1 *a*, Changes in the mean CFF of the nonoccluded eye (●) of the experimental subjects during and after 14 days of monocular deprivation, relative to the changes in the corresponding eye of the control subjects (○). *b*, Changes in the mean CFF of the occluded eye (●) during and after 14 days of monocular deprivation. The increased CFF on postocclusion days 3, 5 and 7 resulted from the aberrant performance of one subject. The baseline difference between the two studies on day 0 is due to the fact that the dominant eye, tested in the second experiment, normally yields a slightly higher CFF value than does the nondominant eye. This difference on day 0, however, was not statistically significant.

effects are long lasting and may persist for a period equal to that of the monocular deprivation duration.

In a second experiment the CFF of the occluded eye (dominant) in eight additional subjects was measured during and after 14 days of monocular deprivation, particularly to determine whether a compensatory depression of the CFF might occur between days 11 and 14, the interval which displays the "step-like" improvement in performance of the nonoccluded eye. The procedure was similar to that used with the previous experimental group except that the occluded eye was now tested. The results (Fig. 1*b*) show no systematic changes in the CFF either during the 14-day deprivation period or in the subsequent follow-up period.

The results of this study, together with those we obtained earlier², indicate that when one eye is exposed to a prolonged period of darkness the performance of the other eye shows a complex temporal pattern consisting of three components or "limbs": an initial depression of the CFF occurring several hours after occlusion, followed by two periods of enhancement or improvement of the CFF—the first up to day 7 and the second after day 9. In an attempt to provide an explanation of this unusual and long lasting visual phenomenon, we have suggested² that it might be placed in the same category as the supersensitivity effects which are known to occur in the higher neural centres after either drug-induced or surgically induced partial deafferentation at the lower levels of the central nervous system, a class of compensatory phenomena which Sharpless⁴, in a recent revision of the law of denervation⁵, has stated result from prolonged disuse of neural pathways. Although our results reported here seem to be consistent with Sharpless's hypothesis, one important question which remains unanswered is the nature of the mechanisms responsible for producing the three components in the CFF performance curve. To provide an answer, it might be fruitful to obtain electrophysiological recordings from various levels of the visual system of the cat or monkey during and after prolonged non-surgical occlusion of one eye and the presentation of appropriate visual stimuli to both the nonoccluded and occluded eye. Only this type of parallel study may be able to throw some light on the specific mechanisms underlying this unusual interocular phenomenon.

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Hydromechanics of Fish Schooling

VARIOUS explanations for fish schooling have been put forward¹, including the rate of predation^{2,3}, social⁴ and genetic¹ factors. Hydrodynamical effects appear to be important to obligate schooling species. They commonly show migratory movements⁴, and the schools usually consist of individuals of the same size range^{6,7} (with similar cruising speeds, as these depend on body-length) swimming in synchronization and in regular arrays⁸. The endurance of the fish is found to be increased twice to six times when in schools¹⁶. These factors may have practical significance, as many commercially important species are found in schools and knowledge of their possible speed and stamina can help design efficient fishing gear.

Breder⁵ mentioned some hydrodynamical effects, but presented no analysis of the advantages of swimming closely together in a synchronized manner, which is one of the definitions of schooling⁴. Belyayev and Zuyev¹⁶ have suggested that wake interactions of closely situated fish may reduce the hydrodynamic resistance of individuals in the school, and have experimental results¹⁷ to support their hypothesis. This and other hydromechanical advantages of the close aggregation of swimming fish are examined here. A very large school will appear boundless to a fish swimming inside. I have examined the effects of surrounding fish on a typical test individual in a school moving at constant velocity (including migratory movements and keeping position in currents).

Single fish swimming in shallow waters shed a two dimensional thrust-type⁹⁻¹¹ trail of vortices of alternating sign (Fig. 1). A shallow basin of water is hydrodynamically equivalent to one horizontal layer of the fish school, which can be treated as a two dimensional situation. (Detailed analysis and discussion of quantitative results are in preparation.)

The vortex trail shed by fish A (Fig. 1) induces a water velocity relative to the vortices, which is opposite to the swimming direction immediately behind the fish, and in the direction of swimming outside the vortex street. A fish situated directly behind A would experience a higher relative velocity and would have to exert extra energy. In position B, however, a smaller effort is required and may even be less than that of a solitary fish swimming at the same speed. The best position has been calculated to be midway (laterally) between two fish of the preceding row. Reductions in relative speed of up to 30% were obtained between the best and worst lateral positions of fish B. As the thrust (which is equal to the drag for steady swimming) is proportional to the square of the velocity, there are advantages in swimming in a diamond pattern (Fig. 1). In this formation, when the lateral distance between adjacent fish is twice the width of the vortex trail, wakes from two successive lateral rows of fish are cancelled.

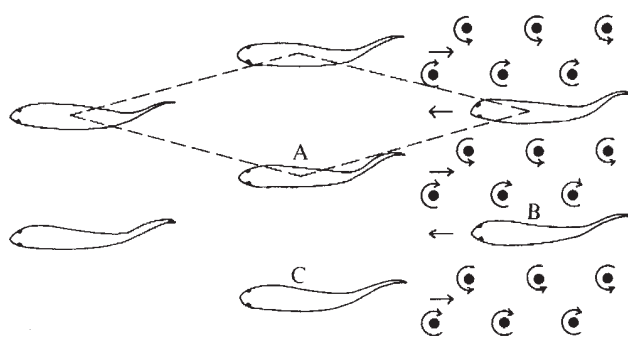


Fig. 1 Part of a horizontal layer of fish in a school, from above. Arrows near vortex streets show direction of induced flow relative to the vortices. The dotted line shows a "diamond" pattern.

The third row will encounter a uniform flow and the total energy saving to the school is half the relative gain to the second row. The situation is similar but more complicated for other ratios of lateral distance to trail width.

Belyayev and Zuyev¹⁶ suggested a configuration similar to that of fishes A and C in Fig. 1, but interpreted this only as a mechanism for obtaining "neutral" rows of vortices (that is, producing neither thrust nor drag) by expansion of the lateral distance between vortices. It has been shown¹² that the lateral spacing of vortex "streets" is stable for all spacing ratios when parallel "streets" are as close as those found in fish schools. My suggestion seems more reasonable as it also explains the "diamond" pattern actually found¹⁴.

The velocities induced on neighbouring fish to the sides and front are negligible because the velocity field of a potential vortex is proportional to the inverse of the distance from the vortex. The force produced by each fish, however, is influenced by the presence of the neighbours in the same lateral row. This configuration may be compared to a single fish swimming in a rectangular vertical channel, whose dimensions are the distances between two adjacent fish centre-lines, laterally and vertically. Rosenhead¹² has shown that the drag of a body shedding a vortex trail in a confined stream is enhanced by the presence of the barriers. Modified, this can also be shown to be the case for thrust due to oscillatory movements of the fish. This results in another hydromechanical advantage of close aggregation. The thrust of each individual fish may be increased by tens of percentages, without any change in the propulsive cycle and energy expenditure. This factor is dependent on the distance between fish, as the relevant term in the expression for the force¹² is proportional to an integral of the square of the induced velocity. These contributions effectively disappear when the lateral distance between fish is more than one length apart.

I finally considered the effects of neighbouring fish above and below my test specimen. Many obligate schooling species are slender⁴ (the length is greater than any other dimension). Newman's¹³ analysis of lateral motions of slender bodies in channels is applicable, by representing the surrounding fish by streamline "walls". This requires that fish of successive horizontal layers are directly underneath each other. The forces produced by a given motion may be increased as much as 15% when the vertical distance between fish centre-lines is twice the cross-sectional depth, and 30% when this distance is only 1.5 times the fish depth¹³. This analysis applies also to a one-layer school moving in shallow waters.

These arguments show that hydromechanical factors can play an important role in schooling behaviour of aquatic species. Although this characteristic may have originated for other reasons, significant advantages may be obtained by proper synchronization of movements and correct regular positioning of individuals. The highly nonlinear dependence of all three factors mentioned on the inter-fish distance results in any irregular spacing being wasteful.

The mechanisms of hydromechanical interaction suggested here are highly idealized due to the inviscid flow model, the reduction to two dimensional analysis and the requirement of perfect synchronization of movement. In actual fish schools these effects would probably be smaller as these requirements would be only partially fulfilled. In a calculation, for example, assuming that laterally neighbouring individuals swim in antiphase (when fish *A* is curved to the right, fish *C* deflects to the left), the effect of the first two mechanisms was reduced by an order of magnitude for this case. Also there is cross-coupling between the effects. The lateral influence decreases the shed vorticity required for moving at a given speed, so that the change in induced velocity (streamwise effects), which is proportional to the vortex strength, is decreased.

Hydrodynamical factors may even explain the inclusion of individuals of up to 50% length difference in certain schools⁷. Otherwise, this would imply that the smaller fish would have to swim at much higher speeds than the usual cruising speed of 3 fish-lengths per second¹. Experimental data^{5,8} show regular formations; when fish were swimming the diamond pattern¹⁴ occurred, but disappeared when they stopped. Measured distances between adjacent fish^{15,17} are of the right magnitude for the suggested hydrodynamical interactions. Additional data, especially of fast swimming large three dimensional schools with accurate estimates of inter-fish spacings in all directions and sustained cruising speed, are required to determine to what extent the mechanisms described here are actually utilized.

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Phytotoxicity of a UHF Electromagnetic Field

It is known that ultra-high frequency (UHF) fields are selectively toxic to plants and seeds¹, but the reasons for this have not been investigated. We have studied the way in which the toxicity of a UHF field is related to various parameters of seeds by observing the effect of the radiation on germination.

We exposed seeds to a $2,450 \pm 20$ MHz field generated in a Litton cavity chamber by a magnetron of nominal power output 600 W. The samples were placed on a glass shelf 1.5 cm above the floor of the chamber, and we found that the intensity of the radiation was such that a 50 ml. sample of water exposed for 60 s absorbed 270 J g^{-1} .

We exposed dry seeds in glass Petri dishes so that they absorbed 270 J g^{-1} . Before and after treatment the seeds were kept at a temperature of 32°C in the daytime and 29°C

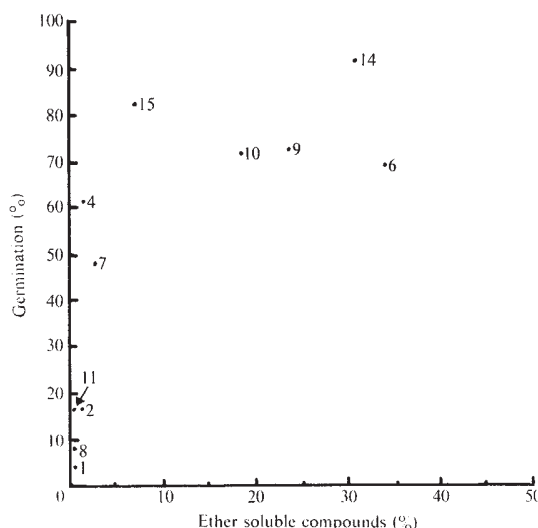


Fig. 1 Relation of susceptibility to a $2,450 \pm 20$ MHz field (271 J g^{-1}) to ether soluble extract of several species. Key to species numbers: 1, Jackbean (*Canavalia ensiformis*); 2, corn (*Zea mays*); 3, bush bean (*Phaseolus linensis* var. Henderson bush); 4, sorghum (*Sorghum vulgare*); 5, pigweed (*Amaranthus* spp.); 6, cucumber (*Cucumis sativus*); 7, Honey mesquite (*Prosopis juliflora*); 8, lima bean (*Phaseolus linensis* var. Fordhook 242); 9, cotton (*Gossypium hirsutum*); 10, soybean (*Glycine max*); 11, black bean (*Stizolobium deeringianum*); 12, curled dock (*Rumex crispus*); 13, jungle rice (*Echinochloa colonum*); 14, mustard (*Brassica* spp.); 15, wheat (*Triticum vulgare*).

at night, at a relative humidity of 75%. The light intensity was 1,500 foot-candles and the length of the day was 15 h. Seeds were considered to have germinated if after five days the radicle extended 3 mm, and germination levels were expressed as the proportion which germinated compared with the untreated controls. Each experiment was repeated ten times with ten seeds of several species used each time.

We examined the susceptibility of seeds to the radiation as a function of the mass per seed, the volume per seed, the density of the seeds, the moisture content of the seeds, their specific heat and chemical constituents, and the amount of energy absorbed. Mass was determined for a number of seeds, and volume by observing the displacement when seeds were added to water (before significant absorption took place). Seeds dried at 40°C to a moisture content of approximately 7% were soaked in water for varying periods of time, removed from the water, blotted until the external surface was dry, and exposed to 32 J g^{-1} radiation. Moisture content was then compared to relative susceptibility. The specific heat was measured using standard calorimetric methods².

Seed moisture content can affect specific heat values; the variation was between 9% and 13%. We expect that long-chained polymers or other large molecules present good targets for electromagnetic radiation. Proteins, nucleic acids, fatty acids, starches and sugars are present in plant cells in substantial amounts.

We determined total protein gravimetrically after extraction with 0.1 M and precipitation with 5% trichloroacetic acid³; total nucleic acids were determined using the procedures of Click and Hackett⁴. Ether solubles were determined gravimetrically and soluble sugars and hydrolysable starches spectrophotometrically³. The data were then correlated with relative susceptibilities of the species to the UHF field using a least squares fit to a straight line. Linear correlation coefficients were calculated and tested by computing the probability of attaining the experimental coefficient from uncorrelated data.

Measurements having a linear correlation coefficient greater than 0.5 and probabilities of 10% or less of accidental correlation in 15 species examined (Table 1) were mass per seed, volume per seed, ether solubles, energy absorbed from the

Table 1 Seed Properties with Significant Linear Correlation Coefficients

Characteristic	Linear* correlation coefficient	$a \pm \sigma_a$	Probability† (%)	$b \pm \sigma_b$	Number of data points
Mass/seed	0.62	57.1 ± 8.1	2	-47.7 ± 16.67	15
Volume/seed	0.75	61.9 ± 6.9	0.1	-70.3 ± 17.30	15
Density	0.29	99.3 ± 49.5	35.0	-44.5 ± 41.1	15
Protein (%)	0.42	67.5 ± 14.7	20.0	-3.19 ± 2.43	10
Soluble carbohydrate (%)	0.50	69.5 ± 15.1	15.0	-0.618 ± 0.360	11
Nucleic acids $\mu\text{g/gf wt}$	0.09	55.0 ± 12.5	< 50.0	-0.033 ± 0.137	9
Ether solubles (%)	0.72	27.4 ± 9.8	1.0	1.89 ± 0.61	11
Specific heat	0.13	30.6 ± 44.9	< 50.0	22.1 ± 61.7	10
Absorbed energy/20 g	0.54	150.7 ± 57.9	10.0	-0.029 ± 0.16	10
Energy absorbed/seed	0.76	62.8 ± 8.7	1.0	-0.26 ± 0.08	10
Log (energy absorbed/seed)	0.91	97.8 ± 10.6	< 1.0	-17.5 ± 2.9	10
Water content					
Wheat	0.77	70.5 ± 19.2	2.0	-2.69 ± 0.92	8
Sorghum	0.77	117.3 ± 21.5	2.0	-3.27 ± 1.09	8
Mesquite	0.96	119.7 ± 9.4	0.1	-1.87 ± 0.22	8
Cotton	0.80	115.7 ± 10.3	1.8	-1.26 ± 0.39	8
Corn	0.73	115.9 ± 9.9	3.0	-1.62 ± 0.62	8
Dicots.	0.65	123.7 ± 7.4	0.1	-1.84 ± 0.21	24
Monocots.	0.92	126.6 ± 18.9	0.1	-4.01 ± 0.99	16

* The sign of the linear correlation coefficient is the same as that of b , but only the absolute magnitude is important in our analysis.

† Probability in % that an uncorrelated distribution would give the same results.

field per 20 g of seed sample, energy absorbed per seed, and imbibition moisture content.

Fig. 1 shows a strong correlation of susceptibility to ether soluble compounds (0.72). This might result from some insulating effect of lipoidal material against the field (non-polar substances have a low dielectric constant), or from the decline of a component associated with susceptibility as lipoidal substances increased.

Both specific mass (Fig. 2) and specific volume are strongly related to susceptibility. This strong relationship might be due to the presence of increasing amounts of a component molecule associated with susceptibility in the larger seeds or to volume/surface relationship. It seems that seed density has little influence on susceptibility (Table 1). We cannot explain why large seeds are more susceptible than closely packed small seeds of an equal mass.

UHF fields produce both thermal^{5,6} and non-thermal effects^{6,7} in biological material. At the field intensities used here, it is not possible to distinguish between thermal and non-thermal effects (Fig. 2). If the correlations between increasing water content and susceptibility (Table 1) are entirely due to the physical nature of water in an electromagnetic field, it should be possible to calculate a linear function that will describe susceptibility of all species as the water content is increased. In two of five species, it seems that linear function

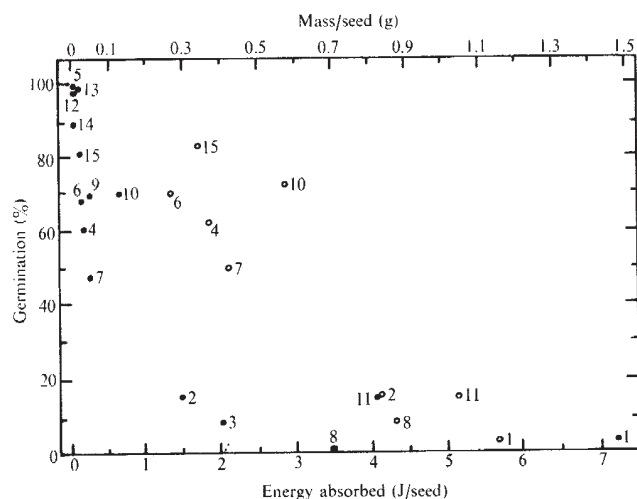


Fig. 2 Relation of susceptibility to a $2,450 \pm 20$ MHz field (271 J g^{-1}) to mass per seed and energy absorbed per seed for several species. Species numbers as in Fig. 1. ●, Data for mass per seed; ○, data for energy per seed.

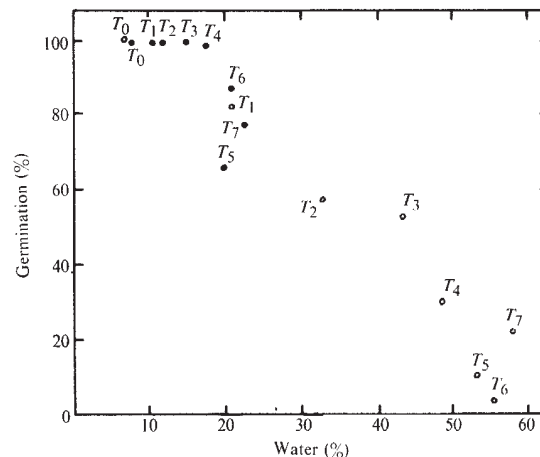


Fig. 3 Imbibition moisture content of seeds as related to susceptibility to a $2,450 \pm 20$ MHz field in corn (○) and mesquite (●). Key to exposure time codes: T_0 , field (32 J g^{-1}) applied immediately; T_1 , field applied after 15 min imbibition of moisture; $T_2, T_3, T_4, T_5, T_6, T_7$, field applied after 30, 45, 60, 120, 180, and 240 min respectively.

is possible while in three species the function is non-linear (Fig. 3). Thus, increasing susceptibility in response to increasing water content does not necessarily follow a linear mathematical relationship. This indicates that the response is mediated by biological factors, for example, internal structure, other molecules which absorb from the field or act as insulators to it, the inherent resistance of cells of a given species to excessive thermal energy, or other unknown factors.

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BOOK REVIEWS

Popper's Third World

Objective Knowledge: an Evolutionary Approach. By Karl R. Popper. Pp. x+380. (Clarendon: Oxford; Oxford University: London, November 1972.) £4.50 cloth; £1.50 paper.

FROM time to time one still meets people who have not yet read Popper's *The Open Society and its Enemies*. My own reaction is to envy them the deeply rewarding intellectual experience they still have ahead of them. *Objective Knowledge* is philosophical in a more austere technical sense of the word, and it will not mean very much to those who are bored by or contemptuous of the discussion of problems which Descartes, Locke, Hume and Kant considered worthy of deep and anxious thought.

Although Popper is a commonsense realist, he dismisses as a subjectivist blunder the commonsense theory of knowledge, according to which knowledge is a specially secure kind of belief and scientific knowledge a specially secure kind of knowledge.

Like Kant, Popper builds anew among the ruins left by David Hume's frightening disclosure that our "knowledge" is not only the nature of belief but of rationally indefensible belief—of an irrational faith. Of this disclosure, as Popper reminds us, Bertrand Russell had already said, perhaps a little too strongly: "The growth of unreason throughout the nineteenth century and what has passed of the twentieth is a natural sequel to Hume's destruction of empiricism."

We are left then with the problem of which "induction" professed to be the solution—the problem of how we come to formulate more or less trustworthy scientific generalizations based upon the evidence of the senses. Popper believes he has solved this problem and his solution as it was propounded in *The Logic of Scientific Discovery and Conjectures and Refutations* is now very widely accepted.

The traditional answer to the problem of how scientific discoveries come to be made has been "by induction". Inductionism is a complex of ill-defined attitudes of thought that defy summariza-

tion, but right at the heart of it lies the belief that there exists a calculus of discovery—a formulary of intellectual behaviour by strict obedience to which we may be led to the formulation of reliable truths concerning the nature of the world around us. Popper has no use for induction; nor had the early Bertrand Russell who wrote (1903): "What is called induction appears to me to be either disguised deduction or a mere method of making plausible guesses."

In Popper's view scientific knowledge is essentially hypothetical in character and scientific laws arise as imaginative conjectures about what the truth might be. The hypotheses in which we come to have the greatest confidence are those which have stood up to the repeated assaults of critical appraisal. From time to time empirical evidence makes it possible to eliminate a hypothesis and thus to discriminate between one hypothesis and another; yet no hypothesis is ever so securely established as to be altogether beyond the reach of criticism and, if need be, of reformulation. This is the great lesson that Popper drew from Einstein's reconsideration of Newtonian principles, which had come to be regarded by most philosophers and scientists as being of virtually apodeictic certainty. Popper has never maintained, as some parodies of his views suggest, that Einstein was right and Newton was wrong—indeed this kind of black and white formulation has no place in Popper's scheme of thought.

If we regard the implications of a hypothesis as its logical "output" then the Popper scheme can be seen to import into methodology the ubiquitous notion of "negative feedback", that is the control of performance by the consequences of the act performed. Another interesting parallel which deserves a fuller treatment than Popper had had time to give it here is the parallel between Darwinian evolution and the autochthonous origin of scientific ideas (compare the autochthonous origin of genetic information)—of scientific ideas which struggle

for their continued existence in the face of repeated criticism and of which only the fittest survive to form the body of received scientific opinion.

Popper has a very good feeling for the conduct of science at bench or shop floor level. For example he says, what all experimental scientists know, that the hypothesis which gives the greatest pleasure when it stands up to criticism is the "risky" hypothesis—the hypothesis that could so very easily have been wrong.

Popper's views are strongly objected to by those who think that the word "hypothetical" is pejorative in character and by methodologists of science who feel diminished by the imputation that they have no inductive method to teach.

The freshest and most original part of Popper's new book is his notion that human beings inhabit or interact with three ontologically quite distinct worlds: world 1 is the ordinary physical world or the world of physical states; world 2, the mental world or world of mental states; world 3 is the world of actual or possible objects of thought; the world of concepts, ideas, theories, theorems and explanations generally, always considered—as we do consider them—objectively, for we do indeed contemplate, discuss, tinker with and propagate these objects of thought. The very imagery we use in discussing world 3 reveals its objective existence outside ourselves, for we "see" an argument, "grasp" an idea, and "handle" numbers expertly or inexpertly as the case may be. The existence of world 3, inseparably bound up with human language, is perhaps the most distinctively human of all our endowments: "I suggest that it is possible to accept the autonomy of the third world and at the same time to admit that the third world originated as a product of human activity. . . ." The third world is not a fiction but exists "in reality". The third world, it may be said, is the greater and more important part of human inheritance; for it is that world which is propagated from generation to generation by tradition, precept, example and deliberate instruction—by

those non-genetical processes of heredity to which Waddington, Huxley and I have often called attention.

Popper writes very skilfully and reasons strongly. Those who are determined not to be persuaded by him had best not read him. Others will find his book a very notable addition to the furniture of world 3.

PETER MEDAWAR

Practical Calculation

Numerical Computation. By P. W. Williams. Pp. viii+191. (Thomas Nelson and Sons: London, October 1972.) £2.50 paper; £5 cloth.

THIS book has material on computer calculations, non-linear, polynomial, linear simultaneous, and ordinary differential equations, finite differences, curve fitting, numerical integration, and eigensolutions. Each chapter has worked examples, some exercises with answers at the end of the book, and bibliographical notes and references.

The book is not meant to be a mathematical text but a guide to good numerical practice; a sound idea, but difficult to achieve. Such a book must be modest in size, and one therefore wonders (a) why the first chapter includes Taylor's series, iteration, convergence acceleration, over-relaxation methods and Aitken's Δ^2 process, (b) why a chapter on polynomials which appear explicitly very rarely in practice, (c) why nothing on ordinary differential equations of boundary-value type, and (d) what principle governed the choice of material for which proofs are or are not given.

Most of the selected material is quite good, and the bibliographical notes are very good. But there are serious exceptions. First, one is irritated by many misprints, a page of numbers with no description, unexplained references to other material, and statements such as "If the Gauss-Seidel method fails to converge then the alternative Jacobi method is available".

More important, there are serious errors of fact and principle. These include incorrect statements on Richardson extrapolation, the need for partial pivoting, the partial instability of the Runge-Kutta method, weak instability, Richardson extrapolation with Simpson's rule, and a catastrophic example 4 on page 158 where the printed numbers are quite wrong and the conclusions quite dangerously fallacious.

I can therefore recommend this book only to those who can study it with the support of expert tuition. The rest should wait, hopefully, for a corrected second edition which could, indeed, be a useful addition to the literature.

L. Fox

Science of Synapses

Structure and Function of Synapses. Edited by George D. Pappas and Dominick P. Purpura. Pp. 308. (Raven: New York. Distributed in the Eastern Hemisphere by North-Holland, Amsterdam, 1972.) Hfl. 75; \$23.50.

Pappas and Purpura on behalf of the New York Society of Electron Microscopists are to be congratulated on the assembly of an authority of authors to write on anatomical, biochemical and physiological aspects of synapses. The book production is good and is marketed reasonably promptly in that the bibliographies include references to the literature of 1970. One may, as is conventional with reviewers today, reflect that the price makes it expensive for students. But it is sturdily built so that it should survive the abuses of the heavy use of the readership of general and departmental libraries.

Each of the twelve articles is by one or more authors distinguished in their special fields; Pappas, Akert, Bodian and Reese on the structure of synapses; Auerbach, Hall, Gerschenfeld and Whitaker on the biochemistry of synaptic transmission; Kandel on the functioning of *Aplysia* central nervous system; Bennett comparing electrical and chemical synaptic transmission; Purpura on the synaptic organization of the mammalian brain and Broom on the development of synapses—is a list of some of the contributors. The student to whom the preface directs this volume can obtain clear and generally balanced summaries of many of the currently active approaches to synaptic functioning. If an undergraduate, the student will need to be an able one because all the articles do deal with their subject in some detail. And in practice, the book is likely to be of most use to post-graduates and research workers in other aspects of the nervous system who want to know current work on synaptic mechanisms but are exhausted by the sight of piles of titles culled from *Current Contents* that yet remain unread.

A reviewer is supposed to criticize, preferably creatively, although in fact the species in general tends to prey on sins of omission and commission. Personally I do not feel like doing this because I find all the articles very worthwhile however much I might sometimes want to give alternative interpretations and emphasis to those problems discussed in this book which I think I understand. But there is one general problem with which books of this kind and most books published on the nervous system these days do not deal. That is the problem of providing general statements and synthèses of how far we have got in understanding the principles by which nervous systems

as a whole work. In fact, a beginner in neural studies may well be put off because she (or he) is likely to find few coherent descriptions of the woods, so full are we with information about the trees. At present mechanisms of neural action have to be studied in this "reductionist" way and it is true, as the preface states, that little can be said about, for example, the mechanisms of memory and behaviour. Yet somewhere along the line "the student" does not need to be put in contact with "the larger picture" if he is to grasp the general importance of the very good work in this kind of collection. Few of us (lacking the confidence and ability of, say, a Sherrington) want, perhaps quite rightly, to write such general articles. Perhaps then a university teacher, uncertain of his role as a projector of facts in this decade of an "explosion of knowledge", can console himself and inspire his audience with enthusiasm by giving a context to the most useful summaries provided by this book.

B. B. BOYCOTT

Ebullient Spectroscopy

Handbook of Commercial Scientific Instruments. Vol. I: *Atomic Absorption.* By Claude Veillon. Pp. xv+174. (Marcel Dekker: New York, September 1972.) \$11.75.

THE purpose of this series is to provide a guide to the purchaser of analytical instrumentation from amongst the many domestic and foreign products sold in the USA. This first volume deals with atomic absorption and surveys seventeen manufacturers' atomic absorption instruments model by model. Its aim is to present a guide to intending purchasers by providing specifications, descriptions, schematic drawings, photographs, details of accessories, approximate prices and so forth. The preface states that all of the information presented is based on material supplied by the manufacturers or their representatives. Subsequently it states that the views and opinions expressed are those of the author alone and no responsibility is accepted for their accuracy by the editor, publisher or instrument manufacturer (or their representatives). Since the author is an editor, this is somewhat confusing.

The author has, however, most certainly provided a valuable survey for intending purchasers. The introduction stresses the important features of various functions of AA instrumentation and explains much of the technical jargon that is bandied about by manufacturers. Whilst these may be elementary to a spectroscopist they might

well be incomprehensible to (say) a biologist needing to buy an AA instrument to study mercury concentrations in lichens or fungi. Ignoring the edited commercial specifications and accounts in the main section of the text, one goes on to the summary provided by the author at the end. Here there are many valuable expressions of opinion and discussions of "pros and cons" of prisms against gratings, meter against digital read-out, single against double beam facility and so on. The author groups instrumentation into categories according to price range, versatility, and so on, and narrows down the field to a fairly simple choice according to the purchaser's budget and requirements. This section has very considerable merit though one cannot but reflect that its value may be rather transient since instruments become obsolete so quickly, and of course the prices can only be regarded as very approximate.

One of the most interesting features is the author's first assessment of the flame emission technique in the second paragraph of the preface and the caveat introduced in the penultimate paragraph of the final section of the book largely due to the strenuous "emission" lobbying of Professor Fassel's group at Iowa State University. It is true to a limited extent that the higher monochromator cost of a good emission instrument is partly offset by the cost of hollow cathode lamps for atomic absorption. But the view expressed that a high-capability emission instrument can easily perform AA is only true when that "expensive" instrument is further provided with the necessary "expensive" power supply and, of course, "expensive" hollow cathode lamps. Emission in flames is certainly a valuable and indispensable technique for trace analysis of elements such as the alkali metals and several others but good emission instrumentation is more complicated to use and it is very doubtful now if it will ever seriously challenge its younger atomic absorption sister for the generality of trace metals analysis. Radio frequency plasma emission methods show a little more promise, but the multielement capability, simplicity and sensitivity of non-dispersive atomic fluorescence spectroscopy are much more likely to offer most challenge to atomic absorption.

This is a useful book but it may become very much out of date very quickly, particularly in this ebullient area of atomic absorption spectroscopy. Other books in the series are proposed for thermoanalysis, nuclear magnetic resonance, X-ray fluorescence, gas-liquid chromatography, mass spectrometry, and so on. If this is a foretaste of the others in the series, I can but reply to the terminal two-word sentence of the text "Good luck" by saying "Thanks a lot".

T. S. WEST

Mathematics in Schools

The School Mathematics Project: The First Ten Years—Being Primarily the Collection of the Directors' Reports for the Years 1961–71. By Bryan Thwaites. Pp. x+266. (London: Cambridge University Press, 1972.) £3 cloth, £1.50 paper.

THE SMP is a splendidly English institution: self-confident, pragmatic, free-enterprise. It started not in a Ministry of Education nor in a faculty lounge but in a Winchester garden. Its initial objective was "the evolution of a syllabus for the whole grammar school range of 11+ to 18, which will adequately reflect the modern trends and usages of mathematics; and the production of a complete set of associated textbooks and teachers' guides". Eleven years and nine directors' reports later, it has produced the books, run an impressive number of courses for teachers, fought and won against universities and examination boards, and expanded to include a wider spectrum of children.

The growth story is a fascinating one, told here in the reports by the project's rumbustious director, Bryan Thwaites. A short article at the end by deputy director Douglas Quadling gives interesting arguments for the inclusion of various topics—linear programming, networks, statistics, matrices, and so on. A great strength of SMP has been its flexibility: the period of self-torture in attempting to do all geometry by transformations is mercifully over, and there is a growing realization that some of the old techniques are still useful after all.

It is easier to criticize than to create. It could be argued that the children should have more relative consideration than the mathematics—how do SMP (and CSM and MME and SMG . . .) judge the degrees of difficulty and appropriateness of their selected topics? How, in fact, do children learn? But certainly the quickest way to a first answer to these questions is to write and see. Another criticism is that SMP has ignored the demands of other subjects, notably physics, but there is an element of "pot and kettle" here, and anyway there was so much to be reformed within a subject without looking sideways. A third criticism could be made of "export SMP"—what is the likelihood of this English venture being really appropriate elsewhere?—but mercifully this seems to be either on the decline or being handed over to the natives for treatment.

SMP will occasionally get its fingers burned (the story of the international project for computing in schools is hilarious, the countries concerned being England and an uncooperative Scotland) but it has played a tremendous role in getting English school mathematics into this century, and trial and

error by dedicated teachers will probably continue to pay off for at least another ten years.

GEOFFREY MATTHEWS

Rational Enquiry

The Pluralist and Possibilist Aspect of Scientific Enterprise. By Arne Naess. Pp. 147. (Universitetsforlaget: Oslo; George Allen and Unwin: London, July 1972.) £4.

PROFESSOR NÆSS can be pleased that the philosophical world is catching up with him. As he reminds us, the Vienna Circle of the 1920s and 30s was a somewhat missionary movement for "rationality" against reactionary forms of metaphysics, and it simply took physics as the paradigm of true knowledge. By contrast, Naess even then appreciated the plurality of genuinely scientific disciplines, and also of theories and approaches within a discipline, as of psychology.

Now, a long time later, he sees himself vindicated by the new pluralistic philosophies of science, notably of Kuhn, but with the implicit agreement of Lakatos. In this vein, he develops some slightly formalized descriptions of scientific choice and change, and also discourses widely over problems in the study of science.

His discussion is most coherent with English-language philosophy of science when it touches on Kuhn and the inescapable relativism of his conception of "scientific revolution" as a clash between incommensurable paradigms. Applying such a scheme to the writing of history and philosophy of science, including Kuhn, he shows that the inevitable paradoxes of self-reference are encountered. But handling these in the light of traditions of methodology of scholarship in general, he arrives at some genuinely interesting conclusions. Among these is that a truly comprehensive and consistent "point of view" cannot be explicitly chosen by an individual (for the conscious choice itself involves criteria belonging to one point of view or another). Hence the real changes that individuals experience in their world-views must occur from a more diffuse set of stimuli, and must proceed through less consistent intermediate stages.

A practical corollary of this conclusion is that pluralism, rather than exclusive domination by one or another system, is the only sane and effective style for science and rational enquiry in general. It is to be hoped that this message can be imparted to Professor Naess's new colleagues in the environmental field (where he now devotes his energies); simplistic philosophies of science are a luxury they cannot afford.

J. R. RAVETZ

Complex Michelin

Chemical Industry: Social and Economic Aspects. By F. R. Bradbury and B. G. Dutton. Pp. ix+236. (Butterworth: London, October 1972.) £2.90.

EXPERTS assure us that in the not too far distant future the chemical industry will be Britain's single largest generator of wealth. Already it is among the leaders and its products have wrought profound changes in the general style of life. The industry has also had its share of criticisms of varied validity. In this interesting, no-nonsense, although somewhat misleadingly entitled book, two insiders explore the realities of successfully operating a major industrial enterprise.

The greatest public noise in recent years had been generated by those whose suddenly sensitized consciences discovered the environmental harm any industrial activity is liable to do. It is a welcome corrective to discover reality behind the slogans; that industrial activity is a matter of choosing the correct shade of grey rather than a re-run of *Paradise Lost*. Industry contributes to national wealth and thus to a high level of creature comforts the developed world has grown accustomed to, but it does so within the ideas, constraints and conditions imposed by society.

Perhaps it is a matter for emotional regret, but the work of industry does not ultimately depend on the inspired inventor leaping out of his bath, but rather on the patient cumulative efforts of solid, conscientious citizens. Thus Bradbury and Dutton, ex-ICI and ICI respectively, are particularly interesting on the multifarious skills needed all the way from production to final use; the roles of marketing and selling strategy, the tortuous route which takes a burgeoning idea to a multi-million pound factory complex, the use of complex analysis to achieve the correct compromise.

The social effects of the chemical industry are complicated and wide ranging and the current debate has progressed beyond considering the undoubted excellence of synthetic fibres and the existence of pharmaceutical products. It would have been illuminating if the book could have mirrored the concern of industry with secondary effects on society, both good and ill, and the change of values mediated through industry.

The book has been written principally for school leavers and their teachers. They will find an excellent Michelin guide to the complexities of modern industry, but rather less of the human excitement and concern which ought to be emphasized if industry is to obtain its share of the best in the age group.

There is a chapter on the individual in industry, but it is rather like a syllabus, a skeleton instead of the living animal. Yet there are plenty of facets to excite the humanistically inclined school leaver; for example, the generally excellent labour relations in the chemical industry and the sophisticated ideas now put in practice to make repetitious jobs more interesting and satisfying. Where are the great human battles that signalled nearly every major development, that gallery of larger than life figures that the chemical industry can boast of, men who may not have known anything about discounted cash flows but pitted their vision against existing society? And, indeed, where are the spectacularly bad decisions that are occasionally made *pace* computers, decision trees and risk analysis? In the last resort, industry and the effects of industry encompass but go far beyond machinery and techniques. They make statements about men in society, about hopes and realities, ambitions and prices paid for them. P. J. FARAGO

Pesticides as Pests

Environmental Toxicology of Pesticides. Edited by Fumio Matsumura, G. Mallory Boush and Tomomasa Misato. Pp. xiv+637. (Academic: New York and London, August 1972.) \$17.50.

THIS book contains the published version of twenty-nine papers read at a United States-Japan seminar held in Oiso, Japan, in October 1971. This is not evident from the title, yet of the forty-eight contributors to this book, twenty-nine work in Japan, seventeen in the USA, one in Canada and one in Britain. Accordingly, what is being offered by Academic Press as a comprehensive work has cut out potentially valuable review articles from scientists outside the USA and Japan. One can imagine how much better this work could have been if, after using the conference as a basis, additional contributions had been obtained to fill the gaps in coverage.

Within these reservations, however, the book contains valuable contributions. The first three chapters deal with the impact of pesticides in Japan, United States and Britain, and these well prepared contributions vividly illustrate both the differences in uses of pesticides in these countries and their respective governments' action in monitoring and limiting the use of certain chemicals.

Further chapters consider mercury in the environment, chlorinated hydrocarbons, fungicides, organophosphates and carbamates. Other sections deal with light and microbial degradation of

pesticides and the toxic effects of pesticides on wildlife. The final section, which is far too brief, skims over the considerations and feasibility of designing new pesticides. In this last section, very little information is given on insect sex pheromones and the reader is left with the incorrect impression that these substances are only known from Lepidoptera.

I have two general criticisms of the book. First, a work like this needs a well constructed index. Unfortunately this is not supplied. The index lists three references to methylmercury and only one for DDT, while BHC, dieldrin, endrin, aldrin and DDE do not even appear. Second, if this book is meant to include a review of the present situation, then I am afraid a number of persons have a poor knowledge of the literature. I hope and believe that scientists in Europe working in this field have a greater knowledge of international published work.

In general, this is a useful contribution, but it could have been so much better. J. C. COULSON

More Spectroscopy

Journal of Electron Spectroscopy. Edited by C. R. Brundle and T. A. Carlson. Volume I. Number I. Pp. 112. (Elsevier: Amsterdam, October 1972.)

DURING the last decade electron spectroscopy has become one of the most important techniques for the investigation of the electronic structure of matter. It has given information on the inner orbitals of molecules and the band structure of solids which has hitherto been unobtainable by conventional "photon" spectroscopy. The literature in the field has expanded to the point which has justified the initiation of this new bimonthly devoted to the subject.

The main fields it embraces are X-ray and ultraviolet photoelectron spectroscopy, electron energy loss spectroscopy, Auger spectroscopy and Penning ionization spectroscopy. Papers covering instrumental aspects, analytical applications, theoretical calculations of electronic structure, photoionization studies by mass spectrometry or ultraviolet absorption as well as relevant work on X-ray absorption and fluorescence are also acceptable for publication.

The first two numbers of this bimonthly journal have already appeared. They contain valuable articles by established workers in various branches of electron spectroscopy. If the quality is maintained in future issues there is no doubt that the journal will provide a unifying medium for many closely related techniques in electron spectroscopy.

W. C. PRICE

Soviet Environment

Conservation in the Soviet Union. By Philip R. Pryde. Pp. xv+301. (Cambridge University: London, November 1972.) £5; \$12.50.

ENVIRONMENTAL problems are becoming increasingly world wide and in need of a global approach. Little progress can be made to their solution, however, until each particular country has learned to manage its own ecosystem. The many different realms within "Spaceship Earth" differ markedly one from another, not only in physical characteristics and economic structures but, more importantly perhaps, in political ideologies, cultural traditions and in aspirations.

The Soviet Union is one such realm. With more than one-sixth of the Earth's land surface it is deeply concerned with the many problems related to the judicious management of its bountiful, but by no means inexhaustible, biotic and mineral resources. There are instances where damming, diverting, polluting, channelling, draining and other alterations in the aquatic environment have resulted in very adverse effects on important fishing resources. Forest felling has encouraged soil erosion, eliminated wild life habitats, increased stream sediment, damaged fish runs and altered local micro-climatic conditions. Surface mining activities have destroyed forests and agricultural lands, induced soil erosion and often seriously polluted nearby streams. Ploughing or grazing on steep slopes, neglect of incipient gullies, improper cropping practices, downslope ploughing, and other poor agricultural practices have contributed to the erosion which now affects two-thirds of the cultivated lands of the USSR.

This study has, as its theme, the contemporary Soviet concern for the conservation of the natural endowments of the country in the face of past and present maltreatment of the environment. Early chapters discuss the historical background of natural resource management in Tsarist Russia and the Soviet Union. The administrative organization governing the use of each broad category of natural resource in the USSR is summarized and some of the major problem areas that have arisen out of the particular Soviet approach are selected for discussion.

Successive chapters deal with land and soil resources, nature reserves, wildlife and fish management, mineral and forestry resources and environmental pollution. The final chapter attempts an evaluation of the contemporary Soviet perception of what constitutes proper natural resource conservation and examines the political and philosophical implications of conservation practice.

One hundred and fifteen of the 300 pages are taken up with an extremely valuable bibliography of Soviet and foreign literature and a large and varied group of appendices covering key terminology, legal documents and resources and environmental data.

Inasmuch as the book represents one of the first broadly inclusive qualitative studies of Soviet conservation practices to be developed outside the USSR, it is to be warmly welcomed. It is unfortunate, though perhaps inevitable, that it should be so expensive.

G. MELVYN HOWE

Exploiting Enzymes

Enzyme Engineering. Edited by L. B. Wingard, Jr. Pp. xiii+415. (Wiley: New York and London, October 1972.) £5.20.

THE thirty reviews, by sixty-one contributors, are based upon two 1971 symposia in the USA. In section 1 the editor defines enzyme engineering as "the sum total of production, isolation, purification, immobilization, and uses of enzymes in a variety of reactor geometries". This section also includes valuable "Recommendations for Standardization of Nomenclature in Enzyme Technology".

The methodology of enzyme over-production by microorganisms, discussed in section 2, is exemplified by the tonnage of proteases isolated. Cellulase utilization should now be seriously examined at large-scale pilot plant level. Dunnill and Lilly, in section 3, illustrate the future with a description of continuous techniques for disruption and recovery by, for example, multistream continuous chromatography, of several enzymes simultaneously. As one alternative to a mechanical technique they disrupt bacteria using lysozyme immobilized on soluble dextran (molecular weight 2×10^6), followed by ultrafiltration. No doubt other uses of soluble immobilized enzymes will follow. For enzyme separations, Porath mentions a new range of amphoteric ion exchangers and evaluates affinity chromatography.

The section on enzyme immobilization omits recent simplified techniques. Attainment of stability may require chemical modification of enzyme prior to immobilization, although Zaborsky disappoints us by providing no details of his own work to which he alludes. Section 5 covers kinetics and performance of enzyme reactors. Apparently, 500 columns, each of 1 ft³ volume of immobilized glucamylase, would replace the total present enzyme production of glucose syrups from corn starch in the USA; but the economics of the process are questionable. On the other hand,

Ford *et al.* describe a 10-ml. capacity recirculation reactor useful for immobilized enzyme kinetics studies.

The book also includes analytical techniques using enzyme electrodes and the potential for microencapsulated enzymes in therapy, and is an invaluable collection of data and ideas in spite of the regrettable absence of widespread commercial utilization of immobilized enzymes to date. The one such application, racemase in Japan, is, however, quoted repeatedly. Where is the profitable return for so much "biochemical ecstasy"? No one is prepared to divulge this yet. Is reactor operation in fact proving too expensive for some? In addition, natural enzymes, or multienzyme systems, may be superseded by synthetic ones sooner than many think (the "time bomb hanging over enzyme engineering"). Nevertheless, the future will be exciting if industry can be induced to make it so. The next symposium in summer 1973 should be fascinating!

This book is good value for money, but its author index is irrelevant and the subject index is almost useless due to its extreme brevity.

B. J. GOULD
A. WISEMAN

Shaping of Plants

Patterns in Plant Development. By Taylor A. Steeves and Ian M. Sussex. Pp. xvii+302. (Prentice Hall: Englewood Cliffs, New Jersey, October 1972.) \$10.95.

THE dust cover announces that this book presents a factual account of the phenomena of development in the vascular plants. The book is not, however, a dry documentation of anatomical events from zygote to adult. Instead it outlines the variations in structure that are encountered from Bryophytes to Angiosperms and presents experimental evidence for how environmental and endogenous chemical and physiological factors are believed to modify the pattern of development. Each of the seventeen chapters surveys a particular aspect of development, setting out the problems for the reader and pointing to areas of understanding which can profitably be expanded by future work. Each chapter concludes with a section of general comment and up to thirty-two selected references.

The essential plasticity of leaf form and regulation of shoot growth in relation to hormones from leaves and stem are nicely presented. The conversion of vegetative to reproductive apices is related to the change from indeterminate to determinate growth and is linked to biochemical activities of the meristem itself. The similarities and differences

between root and shoot meristems are skilfully outlined as are considerations of differentiation of the plant as a whole. The origin and development of vascular elements, the special types of cells of which they are composed, and the role of hormones and sugars in their initiation are given considerable space. Two important chapters cover the formation and function of the cambium and the final chapter deals with totipotency and regeneration.

Throughout the book the question, "How do all these cell types differentiate in a coordinated way to produce the integrated, functionally efficient organism?" is presented and expanded in a particularly lucid and interesting way. The experiments described are well chosen to illustrate questions in plant development rather than to provide answers that are yet in doubt. The chapters on embryogenesis, the shoot apex and the origin of leaf and bud primordia are excellent examples of this approach. Now that there is already so much for the scientist to read, these authors must be congratulated on providing a valuable book that cannot fail to stimulate thought in students and research workers and arouse the interest of all those who work with plants.

DAPHNE J. OSBORNE

Quantum Mechanics

Quantum Mechanics: Principles and Formalism. By R. McWeeny. (*The International Encyclopaedia of Physical Chemistry and Chemical Physics, Topic 2. Classical and Quantum Mechanics Vol 1.*) Pp. xi+155. (Pergamon: Oxford and New York, 1972.) £3.50.

ANOTHER "Introduction to Quantum Mechanics"? One's worst fears are aroused, for surely there are already quite enough of these. But Professor McWeeny's book justifies itself, and one's preliminary fears are not realized. First, as the author says, this is not an introduction, for the basic ideas of the quantum theory are assumed: it represents a revision course, with the opportunities that any revision course provides to give a more consistent account than is possible when the material is first being introduced to the student. Second, although its scope is limited (no one should try to say everything in 150 pages), it is definitely oriented towards the budding theoretical chemist rather than the theoretical physicist or applied mathematician; and to that extent it is not in competition with many other accounts of quantum theory.

Professor McWeeny writes as a master of his subject, with considerable form and control. He also writes well,

so that this book is a pleasure to read. Its compass is limited, and we are told that it is to be the first of a sequence of four volumes dealing with the principles and techniques of quantum mechanics. With such a writer it would surely have been far better to let him write one large volume. The result would have been cheaper (this whole encyclopaedia is far too expensive for the very people it best serves): and he should not have had to stop short after an admirable account of transformation theory, momentum representation, single-particle spin, and the properties of linear operators in Hilbert space, waiting for successive volumes to deal with perturbation theory, group theory, many-body theory and scattering theory. Within the "brief" that he was given Professor McWeeny has done a splendid job: but the brief was not big enough.

C. A. COULSON

Metal π -Complexes

Metal π -Complexes. By Max Herberhold. Volume 2. *Complexes with Mono-Olefinic Ligands.* Part 1. *General Survey.* Pp. xv+643. (Elsevier: Amsterdam, London and New York, 1972.) Dfl. 250; \$78.25.

THE author of this volume comes from a laboratory famous for its work on metal π -complexes—the Technische Universität, Munich. This present volume, Part 1, deals with the history of the subject and the earlier views on bonding; general methods of preparation follow. The main body of the text is devoted to a detailed systematic survey of mono-olefinic complexes. The main emphasis is placed on preparative aspects, but physico-chemical properties are quoted wherever necessary for an understanding of the structure. The olefins have been subdivided into hydrocarbons, for example, ethylene, and those possessing functional groups, for example, acrylonitrile. Spectroscopic and diffraction data, stability constants, current views on metal olefine bonding and uses in homogeneous catalysis, are promised for the second part.

The present volume includes the literature up to the end of 1968 (an appendix gives abstracts of 210 important papers which appeared during 1969 and 1970). I sympathize with the difficulties experienced in the writing and production of such a volume, but potential purchasers ought to know that the systematic literature survey ended about three and a half years ago.

About 1,900 references (which refer to both volumes), together with author and subject indices, are provided. The book is well written and translated. It contains a wealth of material, much of

it in tabular form, and should provide a most useful reference work for the research worker. The very fact that the book is so detailed makes it relatively unsuitable as a teaching monograph for students. My main complaint is at the price: volumes of similar size are currently published at a price half or less of the present book. Otherwise, it can be recommended to workers in the field.

R. A. SHAW

Phosphorus Chemistry

Phosphorus - Nitrogen Compounds: Cyclic, Linear and High Polymeric Systems. By H. R. Allcock. Pp. xiv+498. (Academic: New York and London, May 1972.) \$24.50.

THIS book has been written by a research worker who has made notable contributions to the subject, particularly in the field of high polymers. It is exceedingly well written; the style is clear and concise, and the account of the subject is balanced and critical; it is remarkably free from mistakes.

The volume deals with monomeric, cyclic oligomeric, and polymeric phosphazenes, as well as with phosphazanes. The author develops the thesis (shared by several crystallographers active in the field) that the conformations these molecules adopt are dominated by steric factors rather than by π -bonding, that is, that the bonding adjusts itself to the stereochemistry rather than the reverse.

One point which the author touches upon briefly and which undoubtedly will attain greater significance in the future is the differentiation between those properties of the molecules measured in the ground state, for example, by X-ray crystallographic, nuclear quadrupole and nuclear magnetic resonance studies, and those where the distribution of electrons, and possibly also the shape of the molecule, has been changed either by electronic excitation or complex formation, for example, in basicity studies.

The appearance of the volume is extremely opportune as phosphazenes seem to have broken through the inertial barrier and are beginning to fulfil their long foreseen industrial uses. They are now being manufactured on a considerable scale and have achieved *inter alia* uses in flameproofing.

The book can be highly recommended to the teacher as well as the research worker—academic and industrial. It can be recommended for student reading, although it is somewhat long for an undergraduate course. In view of the rapidly rocketing cost of books, the price is not excessive.

R. A. SHAW